FACULDADE DE ENGENHARIA DA UNIVERSIDADE DO PORTO

Detection of Loss of Consciousness Towards Personalized Anesthesia Induction and Maintenance

Ana Isabel Leitão Ferreira



Doctoral Program in Biomedical Engineering

Advisor: Joaquim Gabriel Magalhães Mendes, PhD
LAETA/INEGI, Faculdade de Engenharia, Universidade do Porto

Co-Advisor: Catarina Sofia da Costa Nunes, PhD
Departamento de Ciências e Tecnologia, Universidade Aberta, Delegação do Porto

Clinical-Advisor: Pedro de Pinho e Costa Amorim, MD
Centro de Investigação Clínica em Anestesiologia, Centro Hospitalar do Porto

April 9, 2021

© Ana Isabel Leitão Ferreira, 2021

Detection of Loss of Consciousness Towards Personalized Anesthesia Induction and Maintenance

Ana Isabel Leitão Ferreira

Doctoral Program in Biomedical Engineering

April 9, 2021

Acknowledgements

The work developed during the course of this doctoral program, and here presented, was possible with the contribution of a wide group of people that somehow touched me during this period, and to only some of whom it is possible to give particular mention.

Let me begin by thanking the support and scientific rigor forwarded by my advisor Prof. Joaquim Mendes, as well as for the refreshing look and tireless meetings with my co-advisor Prof. Catarina S. Nunes.

My special thanks to the person who introduced me into the hospital environment and gave me a privileged knowledge on the medical specialty of Anesthesiology, Dr. Pedro Amorim, for his endless enthusiasm for discovery and readiness to face new challenges and projects.

I would like to acknowledge the Centro de Investigação Clínica em Anestesiologia at Centro Hospitalar do Porto, who welcomed me during this period, to the Director of the Serviço de Anestesiologia, Dr. Humberto Machado and to the Director of the Serviço de Neurofisiologia, Dra. Maria Teresa Pardal Monteiro Coelho, for their support in the research studies. I would like to thank the prompt and tireless collaboration of a large group of professionals, who always made available to support data collection performed at the neurosurgery operating room: nurses, surgeons, auxiliaries, anesthesiologists and interns, there were many who contributed for a successful outcome, and to which I leave a warm thank you. I leave my special thanks to Dra Leónia Ferreira, Dra Isabel Alexandra Santos, Dra Manuela Casal, Dra Elizabete Neutal, Dr. Manuel Campos and Dr Francisco Lobo; and to the nurses Maria João, Paulo and Pedro.

I would like to thank all patients who agree to participate in the studies, from whom I always received the maximum collaboration. I also would like to acknowledge to Dr. Márcio Cardoso and to João Anselmo, for their expertise and collaboration.

I was fortunate to find several willing and interesting friends during the course of this work, I would like to leave a particular warm mention to my team mates, Rui Correia, Sérgio Vide, Mafalda Couto, Ana Castro and Aura Matias, who attended over the years always with a friendly word and encouragement.

To all my friends (they know who they are!), for the friendship and good years in the university, and to my friend António Ramos, who accompanied me since the first steps in of my journey. A special and caring thank you to Francisco Dias for the love, resilience, patience and companionship that carried and kept me going in the hard moments.

I thank for my family, in particular my parents and sisters for all the dedication and unconditional love. My eternal gratitude and love.

Last but not the least, I would like to acknowledge the financial support provided by the Fundação para a Ciência e Tecnologia, Portugal (SFRH/BD/98915/2013), for the scholarship which allowed my dedication in full time to the development of this thesis.

Ana Isabel Leitão Ferreira

Resumo

A anestesia geral consiste na indução farmacológica de uma alteração do estado de consciência necessária para a realização de diferentes procedimentos cirúrgicos. Esta engloba um conjunto de efeitos reversíveis na consciência, cognição, sensação, respostas motoras e no sistema nervoso autónomo.

Embora a anestesia geral seja convencionalmente categorizada em diferentes componentes (hipnose, analgesia e imobilidade), os fármacos geralmente utilizados têm habitualmente mais do que um efeito. Portanto, é fundamental monitorizar os diferentes componentes de forma independente e em simultâneo, de modo a permitir a compreensão da complexidade individual e a orientação, para cada paciente, dos efeitos da anestesia geral.

A base para uma correta administração de fármacos é constituída pela capacidade de medir os diferentes efeitos de um fármaco. Embora possa parecer simples distinguir um indivíduo consciente de inconsciente, existem diferentes estados intermédios (e mesmo a própria inconsciência gerada através de fármacos possui diferentes estados), tornando muito difícil determinar a inconsciência com o auxílio de dispositivos baseados em eletroencefalografia. Estes dispositivos adquirem e processam a atividade eletroencefalográfica, fornecendo um índice calculado para orientar a administração dos fármacos hipnóticos. Ainda que tenham um papel relevante na prática clínica, estes dispositivos comerciais disponíveis para monitorizar a atividade cerebral não discriminam com precisão a transição entre o estado de consciência e o estado de inconsciência, pois o seu funcionamento é baseado na análise de sinais eletroencefalográficos e não na consideração da conetividade e comunicação cortico-cortical, o que pode limitar a sua aplicabilidade durante a indução da anestesia geral.

Com o intuito de melhorar a personalização da anestesia e os resultados clínicos, esta tese tem como objetivo estudar diferentes abordagens que otimizem a monitorização e administração de fármacos hipnóticos. A investigação resultante desta tese incluiu a avaliação de diferentes abordagens para monitorizar e titular a hipnose; estudar a transição consciência/inconsciência, procurando tecnologias capazes de individualizar a indução anestésica e discutir métodos capazes de determinarem os efeitos que os fármacos anestésicos podem ter na hipnose durante o período peri-operatório.

Abstract

General anesthesia is a reversible drug-induced state of altered arousal required for different types of procedures, involving a series of changes in the body that alter consciousness, cognition, sensation, motor responses, and autonomic control.

Although general anesthesia is conventionally categorized into different components (hypnosis, analgesia, and immobility), drugs used usually have more than one effect. Therefore, monitoring the different components independently and simultaneously is required to understand individual complexity and guide, to each patient, the personalization of the different anesthesia effects.

The basis for proper drug titration is to be able to measure different pharmacological effects. While it may seem straightforward to distinguish a conscious and unconscious individual, there is an endless number of stages in between, and even the unconscious has several stages, rendering it very difficult to determine with available electroencephalogram-based devices. These devices acquire and process the electroencephalographic activity, providing an index computed to guide hypnotic drug administration. Whilst definitely useful, commercial brain monitoring devices do not accurately discriminate between consciousness and unconsciousness because their functioning is based on electroencephalographic signal analysis rather than consideration of corticocortical connectivity and communication, which might limit their application during anesthesia induction.

To contribute to the development of anesthesia personalization, this thesis aims to explore different approaches that optimize the monitoring and administration of hypnotic drugs, with the goal of improving perioperative outcomes. The research comprised here aims to evaluate different approaches to monitor and titrate the hypnotic component of general anesthesia; to study the transition between consciousness and unconsciousness, by exploring for technologies capable of individualizing anesthetic induction and discuss methods capable of determining the effects that anesthetic drugs may have on hypnosis during the perioperative period.

To my lovely family.

Table of contents

1 INTRODUCTION 1

1.1 Motivation 3

1.2 Methodology framework 4

1.3 Relevance and contributions 6

1.4 List of Publications 6

1.5 Thesis Outline 11

2 LITERATURE REVIEW 13

2.1 Propofol administration in the induction phase of general anesthesia in Portugal 15

2.2 Overview of the current methods to monitor the depth of anesthesia and detect loss of consciousness 27

3 PROPOFOL REQUIREMENTS AT LOSS OF CONSCIOUSNESS 43

3.1 Quantification of the inter-patient variability of the amount of propofol required for the loss of consciousness and identification of predictive factors 45

3.2 Evaluation of Bispectral Index time delay in response to anesthesia induction: an observational study 59

3.3 Neuro-fuzzy models to predict the required propofol amount for loss of consciousness during general anesthesia: a preliminary study 67

4 PATTERNS OF HYSTERESIS BETWEEN INDUCTION AND EMERGENCE OF NEUROANESTHESIA 75

5 ELECTROENCEPHALOGRAPHY IN THE DETECTION OF LOSS OF CONSCIOUSNESS 93

5.1 EEG signatures at the transition between conscious and unconscious 95

5.2 Implementation of neural networks to frontal electroencephalography for the identification of the transition responsiveness/unresponsiveness during induction of general anesthesia 103

6 ELECTROMYOGRAPHY IN THE DETECTION OF LOSS OF CONSCIOUSNESS 117

6.1 Electromyographic assessment of blink reflex throughout the transition from consciousness to unresponsiveness during induction 119

6.2 Performance of EMG-derived parameters from blink reflex: prediction probabilities and multinomial logistic analysis 135

7 CONCLUSIONS AND FUTURE WORK 153

7.1 Future Work 156

8 REFERENCES..... 159

Appendix A 171

Appendix B 177

B_1 Clinical Protocol – New scheme for individualizing propofol induction and maintenance of general anesthesia……..……175

B_2 Informed Consent – New scheme for individualizing propofol induction and maintenance of general anesthesia ……..……...185

B_3 Acceptance Letter – New scheme for individualizing propofol induction and maintenance of general anesthesia ...……..……191

Appendix C 197

C_1 Clinical Protocol – Identification and characterization of neuromuscular reflections as indicators of detection of loss of consciousness in induction of general anesthesia with propofol in surgical patients ……..……195

C_2 Informed Consent – Identification and characterization of neuromuscular reflections as indicators of detection of loss of consciousness in induction of general anesthesia with propofol in surgical patients ……..…….…...207

C_3 Acceptance Letter – Identification and characterization of neuromuscular reflections as indicators of detection of loss of consciousness in induction of general anesthesia with propofol in surgical patients...……..……..……..……211

List of figures

Figure 1.1 General scheme of a system to personalize the propofol concentration by monitoring the three main domains of general anesthesia: analgesia, hypnosis and immobility. In this thesis, the attention was focused on hypnosis because it is where the loss of consciousness occurs. 4

Figure 2.1 Overshoot and hysteresis between plasmatic and effect-site concentration of propofol (mg/mL) versus time for different infusion rates of propofol: A) 1200 mL/h until LOC (14 seconds); B) 200 mL/h until LOC (2 minutes). 29

Figure 3.1 Monitors in the operating room: 1 – INVOS monitor, 2 – ANI monitor, 3 – Dedicated computer with Rugloop Software, 4 – Datex Ohmeda Aisys/GE monitor, 5 – TCI system (Fresenius Base Primea Orchestra). 48

Figure 3.2 Box-plot diagram showing the propofol effect-site concentration at LOC in patients from Group 1, Group 2 and Group 3. 51

Figure 3.3 Anesthesia setup. 61

Figure 3.4 Block diagram of BIS modulation. 62

Figure 3.5 Data results from all 45 patients: a) Effect-site concentration of propofol and remifentanil for each patient during the first 15 min of anesthesia induction; b) Real versus modeled BIS values. 63

Figure 3.6 Time delay (Δt) between the real and the modeled BIS for: a) patient #5, b) patient #19, c) patient #22 and d) patient #27. 64

Figure 3.7 Time delay (Δt) between the real and the modeled BIS for all patients. 65

Figure 3.8 Testing error variability for the Fuzzy Models with smallest mean absolute testing error: Fuzzy Model 1 (25 rules – grid partition), Fuzzy Model 1 (4 rules – subtractive clustering), Fuzzy Model 4 (34 rules – subtractive clustering) and Fuzzy Model 1 (17 rules – subtractive clustering). 71

Figure 3.9 Results of the Fuzzy Model 1 with 25 rules (grid partition), with 4 rules (subtractive clustering) and with 17 rules (subtractive clustering): a) on the training data; b) on the testing data. 73

Figure 3.10 Output surface for the Fuzzy Model 1 using 25 rules. 74

Figure 4.1 Relationship between individual estimated effect-site concentrations of propofol using Schnider's PK model for all patients: (A) Time (in minutes) from starting infusion of propofol until LOR versus estimated effect-site concentration (μg/mL) at LOR; (B) Estimated effect-site concnetration (μg/mL) at LOR versus estimated effect-site concentration (μg/mL) at ROC; (C) Time (in minutes) from stopping infusion of propofol until ROR versus estimated effect-site concentration (μg/mL) at ROR and estimated effect-site concentration (μg/mL) at the moment propofol infusion was stopped. Pearson's correlation test, $p<0.01$ represents a statistically significant correlation. 85

Figure 4.2 Hysteresis. Filled squares and their corresponding best-fit solid curve denote LOR. Open squares and their corresponding best-fit solid curve denote ROR. Within the shaded areas, patients will be awake or anesthetized depending upon their previous state of arousal. These areas represent a resistance to change in the state of consciousness. (A) Propofol dose-response curve in humans for LOR and ROR regarding all surgeries. (B) Propofol dose-response curve in humans for LOR and ROR regarding craniotomies only. (C) Propofol dose-response curve in humans for LOR and ROR regarding spinal surgeries only. 89

Figure 4.3 Simulation of 1000 propofol dose-response curves for estimated plasma concentrations at LOR and ROR, applying the prediction error margins (Interquartile Range (IQ)) published by Glen and White[121] and considering the difference for increasing and decreasing concentrations (LOR vs. ROR). At the top are presented the propofol dose-response curves for LOR and ROR with plasma concentrations estimated by the Schnider model and at the bottom are presented those by the Marsh model. A) and D) All patients; B) and E) Patients presenting for intracranial surgeries; C) and F) Patients presenting for spinal surgeries. 90

Figure 5.1 Dynamics from patient 8 during induction from remifentanil (Ce target of 2ng/mL) and propofol induced unconsciousness: a) Drugs concentrations aligned with respect to LOC; b) EEG spectrogram aligned with respect to LOC; c) Power in gamma (25-30Hz), delta (1-4Hz) and alpha (8-12Hz) bands aligned with respect to LOC. 99

Figure 5.2 Dynamics from patient 9 during induction from remifentanil (Ce target of 2.5ng/mL) and propofol induced unconsciousness: a) Drugs concentrations aligned with respect to LOC; b) EEG spectrogram aligned with respect to LOC; c) Power in gamma (25-30Hz), delta (1-4Hz) and alpha (8-12Hz) bands aligned with respect to LOC. 101

Figure 5.3 BIS Vista™ Bilateral Sensor and Vista Monitor®. Monitoring of the left hemisphere (BIS L). (Photos provided by Medtronic). 105

Figure 5.4 Example of successive 5-second electroencephalographic (EEG) epochs (blue lines) and the corresponding output (LOR or no-LOR) classified by the anesthesiologist. The estimated effect-site concentrations of propofol at each epoch are depicted in the graphic (red line). 110

Figure 5.5 Confusion matrices on applying the classifier on Electroencephalographic (EEG) dataset using cross-validation and using a time window of 5, 10, and 15 seconds. 111

Figure 5.6 Architecture of the convolutional neural network (CNN). The electroencephalographic (EEG) input shape has dimensions 5 x 128 (samples) x 2 (channels) = 1280; the output of the net is dichotomous: 1 (LOR) or 0 (no-LOR). Stochastic optimization was realized using Adam [151] with learning rate=0.0001, and decay=5e-5. As the activation function, the *LogSoftMax* was used. 114

Figure 5.7 Performance of the Deep Neural Network (DNN) model in the test-set of the electroencephalography (EEG). Micro-average area under the curve and macro-average area under the curve are presented by receiver operation characteristics (ROC) curves. 115

Figure 6.1 Patient with the positioned electrodes for stimulation and recording of electrically evoked blink reflexes in the orbicularis oculi muscle. 122

Figure 6.2 Example of an electromyographic record of an electrically evoked blink reflex before the infusion of propofol started (baseline). The highlighted line represents the average response from four consecutive blink reflex responses. Vertical lines mark the beginning and end of the individual components (R1 and R2), these lines were used to calculate latency, duration, area, and amplitude. These lines were marked by an expert neurophysiologist at the end of the session, using the marker tool of the VikingQuestTM neurophysiological device. 125

Figure 6.3 Example of electromyographic records of the average from four consecutive blink reflex responses of one patient. Each row shows the effects of the increasing administration of propofol. Amplitude and area of R1 decreased with the depth of anesthesia. After 138 seconds

of propofol infusion (t), the R2 component disappears. R1 component was last seen after 150 seconds. Loss of behavioral responsiveness (aRASS = -5) occurred after 162 seconds and loss of corneal reflex (aRASS = -6) occurred 168 seconds after propofol infusion, at an effect-site concentration of 5.36 μg/mL. Vertical lines mark the beginning and end of the individual components (R1 and R2), marked by an expert neurophysiologist at the end of the session, using the marker tool of the VikingQuestTM neurophysiological device. 126

Figure 6.4 Values of variations from baseline areas and variations from baseline amplitudes of the first component of the blink reflex (R1) for all patients (n=25) are plotted against the adapted version of the Richmond Agitation-Sedation Scale (aRASS) (A-B) and the estimated effect-site (Ce) propofol concentration (C-D). 127

Figure 6.5 Propofol dose-response curve for loss of R2 (LOR2), loss of R1 (LOR1), loss of behavioral response (LOBR) and loss of corneal reflex (LOCR) regarding all patients. Filled squares and their corresponding best-fit dotted line denote LOR1; crosses and their corresponding best-fit solid line denote LOR2; filled diamond and their corresponding best-fit dashed-dot line denote LOBR and asterisks and their corresponding best-fit dashed line denote LOCR..... 129

Figure 6.6 Effect-site and plasma concentrations of propofol during an intravenous administration with TCI system performed to one patient, female, 65 years old, 75 kg, 160 cm, with an infusion rate of 220 mL/h. Red lines represent the estimated concentrations of propofol, recorded by the TCI system (dashed line representing the effect-site concentrations and dotted line representing the plasma concentration). Blue lines represent the simulated concentrations of propofol, computed if propofol infusion stopped at LOR1 (solid-line representing effect-site concentration and dash-dot-line representing plasma concentration). LOR1 occurred 151 seconds after propofol started and corresponds to the peak maximum of the simulated plasma concentration. LOCR occurred 168 seconds after propofol started and corresponds to the peak maximum of the estimated effect-site concentration. Overshoot corresponds to the difference between the peak of the effect-site concentration and the effect-site concentrations at which the peak plasma concentrations was maximum..... 132

Figure 6.7 Electrode placement for blink reflex monitoring. Electrodes a (cathode) and b (anode) are electrodes used for electrical stimulation. Electrodes c (active) and d (reference) are silver disc recording electrodes. Electrode e is a ground electrode..... 138

Figure 6.8 Examples of electromyographic records of the average from four consecutive blink reflex responses of a) Patient #1: a male patient (60 years, 65 kg), and b) Patient #2: a female patient (47 years, 64 kg) who participated in this study. Each row shows the effects of the increasing administration of propofol. In Patient #1, after 117 seconds of propofol infusion, the R_2 component disappeared. R_1 component was last seen after 126 seconds, loss of responsiveness (aRASS=-5) occurred after 135 seconds after propofol infusion, at an effect-site concentration of 3.93 μ/mL. In Patient #2, after 98 seconds of propofol infusion, the R_2 component disappeared. R_1 component was last seen after 113 seconds, loss of responsiveness (aRASS=-5) occurred after 134 seconds after propofol infusion, at an effect-site concentration of 3.00 μ/mL. 141

Figure 6.9 The predicted propofol effect-site concentration vs adapted Richmond Agitation-Sedation Scale (aRASS)..... 143

Figure 6.10 User interface of the program "Pk Tool" for computing prediction probability (P_k). Left panel refers to the data reading function. In the middle panel, above, is the class and indicators/features selection such as settings for computation and below, is the calculation and result output unit. Right panel indicates the Receiver Operating Characteristic Curve (ROC) only used for dichotomous classes (which is not the case). Results are saved as data sheets..... 146

Figure 6.11 The adapted Richmond Agitation-Sedation Scale (aRASS) vs mean and standard deviation: 1) effect-site concentration (Ce) of propofol; 2) mean frequency (f_{mean} [Hz]) during the time window period T_1; 3) Spectral entropy during the time window period T_1; and 4) Spectral entropy during the time window period T_2. 147

List of tables

Table 2.1 Distribution of the answers to all questions in the questionnaire. 18

Table 2.2 P-values for the Pearson Chi-Square test relating the different questions of the survey. 22

Table 2.3 Recommended ranges for the different EEG-based indices of the hypnotic component of anesthesia. Values are unitless and range from 0 to 100. 35

Table 2.4 Indicative values of the loss of consciousness moment. The values for the loss of consciousness are expressed in "Mean (Standard Deviation)", "Mean (Maximum-minimum)", "Mean" according to the corresponding authors. The acronyms mean: BIS – Bispectral Index; SE – State Entropy; RE – Response Entropy; PSI – Patient State Index; CSI – Cerebral State Index; IoC – Index of Consciousness; AAI - AEP Index. 38

Table 3.1 Demographics from Group 1: induction performed with remifentanil and propofol; Group 2: induction performed with propofol and remifentanil; and Group 3: induction performed with fentanyl and propofol. 50

Table 3.2 P values of Chi-square and student t-tests comparing the studied variables between Group 1 and Group 2. 50

Table 3.3 Inter-patient variability of the propofol Ce concentration required for LOC and in the volume of propofol at LOC, BIS and EMG at LOC for Group 1, Group 2 and Group 3. 52

Table 3.4 Descriptive statistics for the studied variables in Group 1, Group 2 and Group 3. 56

Table 3.5 Correlation coefficients between clinical variables at LOC and the total infused volume of propofol until LOC. 70

Table 3.6 Mean absolute error for the fuzzy models for the total infused volume until LOC for the training and testing data sets. *Using grid partition; +Using subtracting clustering. 71

Table 4.1 Demographic Data From All 45 Patients Divided According to the Type of Surgery. Results are Mean ± Standard Deviation. There Were No Statistically Significant Differences Between the Two Groups (p>0.001). 83

Table 4.2 Propofol, Fentanyl, and Remifentanil Estimated Concentrations at LOR and ROR in All 45 Patients, in the Patients Subjected to Craniotomies Only and in Patients Submitted to Spinal Surgeries. 84

Table 4.3 Propofol and Remifentanil Estimated Effect-site Concentrations During Maintenance, Propofol Estimated Effect-site Concentration When Infusion was Stopped Before the End of the Procedure and Duration of the Procedure. 86

Table 4.4 End-tidal of CO2, Heart Rate and Mean Arterial Pressure at LOR and ROR for All, Spinal and Intracranial Surgeries. Comparisons Were Made Between the Values at LOR and ROR (Paired Student's T-Test or Wilcoxon as Appropriate). P<0.001 Represents a Statistic Significant difference. 87

Table 4.5 Best-fit Parameters for LOR and ROR Sigmoidal Dose-response Curves Regarding All, Intracranial, and Spinal Surgeries. 88

Table 5.1 Patient data regarding drug concentrations (Ce – Effect site concentration) required for loss of consciousness (LOC) and EEG spectrogram. 98

Table 5.2 The adapted Richmond Agitation-Sedation Scale (aRASS). Definition of seven anesthetic stages based on clinical signs. The main clinical signs of each state are referred, as well as the attributed a numerical scale. 106

Table 5.3 Results of cross-validation (average over 10 runs)..... 111

Table 6.1 The adapted Richmond Agitation-Sedation Scale (aRASS). Definition of seven anesthetic stages based on clinical signs. The main clinical signs of each state are referred, as well as the attributed a numerical scale. 123

Table 6.2 Time since propofol started (seconds), predicted effect-site (Ce) concentrations of propofol (μg/mL), and adapted Richmond Agitation-Sedation Scale (aRASS) score at loss of R_2 (LOR_2), loss of R_1 (LOR_1), loss of behavioral response (LOBR) and loss of corneal reflex (LOCR) in all 25 patients. Results are mean ± standard deviation or median. 128

Table 6.3 Predicted effect-site concentrations of propofol (μg mL^{-1}) that produces loss of R_2 (LOR_2), loss of R_1 (LOR_1), loss of behavioral response (LOBR) and loss of corneal reflex (LOCR) in 50% (EC_{50}) of patients..... 128

Table 6.4 Correlations [mean prediction probability (group P_k) and mean Spearman's correlations (group ρ)] between the adapted Richmond Agitation-Sedation Scale (aRASS) score and the areas or amplitudes of blink reflex component R_1..... 130

Table 6.5 Spearman's correlations between the change in areas and amplitudes of the blink reflex component R_1 from baseline to adapted Richmond Agitation-Sedation Scale score -1 (aRASS=-1) and the effect-site (Ce) concentration of propofol at loss of behavioral response (LOBR) and loss of corneal reflex (LOCR) in all 25 patients. 130

Table 6.6 Baseline blink reflex responses in the actual study and in other different studies. 134

Table 6.7 Estimated effect-site concentration of propofol, adapted Richmond Agitation-Sedation Scale values, and times at which LOR_2, LOR_1 and LORP occurred. Results are mean ± standard deviation or median [minimum, maximum]. 143

Table 6.8: Values from the extracted features during two different time windows: P_1- from 10 ms to 25 ms, in which it is expected R_1 to be analyzed; P_2 – from 25 ms to 200 ms, in which R_2 is expected to be analyzed. 145

Table 6.9: Prediction probabilities (P_k) values calculated between the adapted Richmond Agitation-Sedation Scale (aRASS) and the electromyography (EMG) extracted feature. Correlation coefficient R with aRASS and with propofol effect-site (Ce) concentration. T_1 and T_2 are time windows from 10 ms to 25 ms, and from 25 ms to 200 ms, respectively..... 149

Table 6.10: Likelihood ratio tests..... 150

List of abbreviations and symbols

AEP	Auditory Evoked Potential
ANFIS	Adaptive Fuzzy Interference Systems
ANI	Analgesia Nociception Index
ANN	Artificial Neural Network
ANOVA	Analysis of Variance
aRASS	altered Richmond Agitation-Sedation Scale ASA American Society of Anesthesiology
ASA	American Society of Anesthesiologists
AUC	Area Under the Curve
BIS	Bispectral Index
BMI	Body Mass Index
BP	Blood Pressure
Ce	Effect-site Concentration
CHUP	Centro Hospitalar e Universitário do Porto
CI	Confidance Interval
CNN	Convolutional Neural Networks
Cp	Plasmatic Concentration
CSI	Cerebral State Index
DNN	Deep Neural Network
DOA	Depth of Anesthesia
ECG	Electrocardiography
EEG	Electroencephalography
EMG	Electromyography
EP	Evoked Potential
FCN	Fully Connected Neural Network
FDA	Food and Drug Administration
FEUP	Faculdade de Engenharia da Universidade do Porto
FFT	Fast Fourier Transform

FIS	Fuzzy Interference System
FN	False Negative
FP	False Positive
GA	General Anesthesia
GABA-A	Gamma-AminoButyric Acid
HR	Heart Rate
IFT	Isolated Forearm Technique
IoC	Index of Consciousness
LBM	Lean Body Mass
LOBR	Loss of Behavioral Response
LOC	Loss of Consciousness
LOCR	Loss of Corneal Reflex
LOR	Loss of Responsiveness
LOR_1	Loss of R_1 Response
LOR_2	Loss of R_2 Response
LORP	Loss of Response
MLR	Multinomial Logistic Regression
NIRS	Near Infrared Spectroscopy
NMDA	N-methyl-D-aspartate
OAAS	Observer's Assessment of Alertness and Sedation Scale
PD	Pharmacodynamic
PK	Pharmacokinetic
PSD	Power Spectral Density
PSI	Patient State index
RASS	Richmond Agitation-Sedation Scale
RE	Response Entropy
ROC	Recovery of Consciousness
ROR	Recovery of Responsiveness
SAP	Systolic Arterial Pressure
SD	Standard Deviation
SE	State Entropy
SpO_2	Pulse Oximetry
SPSS	Statistical Package for the Social Sciences
TCI	Target Controlled Infusion
TN	True Negative
TP	True Positive
TSK	Takagi-Sugeno-Kang

1 INTRODUCTION

Anesthesia is a medical field that has rapidly evolved in recent years, accompanying the technological developments and the tools they carried. General anesthesia (GA) is a complex combination of drugs to induce a state of hypnosis, analgesia, and immobility, with concomitant stability of the automatic, cardiovascular, respiratory, and thermoregulatory systems [1]. Different anesthetic drugs are commonly used to achieve a GA state, such as hypnotics, analgesics, and muscle relaxants. Of the GA components, hypnosis is the most fascinating and is the focus of this thesis.

Although many years have passed since the first GA demonstration in 1846 by William T. Morton in the "Ether Dome" of Massachusetts General Hospital in Boston, the mechanisms by which general anesthetics can render an individual unconscious remain incompletely understood [2].

Several drugs are known to produce hypnosis, but propofol is the most commonly used. Propofol acts on γ-aminobutyric acid type A (GABA-A) receptors. Although the hypnotic effect can be achieved with it, propofol can be administered based on pharmacokinetics, which predicts what the body does to a drug. Most of these models may even extend the modulation of an effect-site compartment that facilitates the hypnotic administration. However, to achieve precise drug titration, the quantification of pharmacodynamic effects must obtain a personalized and tailored approach [3].

Gathering the concept of personalized anesthesia and its hypnotic component suggests an important question: developing approaches that can provide the correct hypnotic dose to each patient during induction

and maintenance of general anesthesia. This question has not yet received the attention it deserves. Induction of anesthesia is still widely performed in the way it was when intravenous agents became available, which is a quick manual administration of a bolus based on the patient's weight. Few scientific evidence or pharmacology knowledge has been used to change this practice. Bringing together information from both pharmacokinetics (PK) and pharmacodynamics (PD) during the induction phase and studying the emergence phase as well, might bring the possibility to improve drug delivery during maintenance and thus be important to one achieve a personalized hypnotic effect.

Assisting in the titration of hypnotic drugs during maintenance is possible due to the currently available depth of anesthesia (DOA) monitors. A good correlation exists between drug concentrations and the processed indexes values. However, for the induction of anesthesia, such monitors are not the best choice as they have an excessive processing time delay. If induction is performed by a manual bolus, the patient will lose consciousness rather quickly because the rapid bolus results in a significant overshoot in the cerebral concentration, a fall blood pressure, and an excessive drop in the DOA index. The anesthesiologists tend to believe an adequate amount of propofol is given based on the fact that loss of consciousness (LOC) was almost simultaneous with stopping the bolus. The alternative is to administer propofol for induction in a manner that will attenuate this overshoot. The use of Target-Controlled Infusion (TCI) anesthesia allows the setting of a cerebral concentration target that can be used for induction. However, there is no way of knowing, for an individual patient, what concentration will be needed to lose consciousness during the induction phase of general anesthesia. A solution is to start by setting an initial low target and to increase it stepwise while assessing consciousness frequently. This technique will result in spending several minutes to achieve the LOC since, at every concentration step, one has to wait for its respective steady-state to occur. A good option may be if the LOC occurs at a low cerebral effect-site concentration of propofol. In this manner, induction is performed by the infusion of propofol at 20-40 mg/kg/h [4][5], and LOC is assessed every 10 seconds. At the time of LOC, the propofol infusion is stopped, the effect-site concentration predicted by the PK model in use is noted and the TCI system is switched to effect-site TCI mode. A target effect-site concentration is set, equal to that of LOC, or lower than that, titrated by the DOA monitor. Even though the infusion rate is much lower than the infusion rate of a manual bolus, overshoot still occurs, although much smaller, the magnitude decreases with increasing LOC concentrations. This technique results in an average induction time of around 3 minutes, quite acceptable regarding the total anesthesia time and when considering what is gained by individualizing a patient's need. If one does not have access to a TCI system, this induction method can still be used. In that case, following the LOC, the anesthesiologist should set-up a manual infusion, titrating propofol to the DOA index.

All the above is based on pharmacology studies [5], and the clinical practice presented here is an option for the attempt to individualize induction, which is "personalizing the effect". It should be seen not as evidence but mostly as an example of a possible way to personalize anesthesia induction, motivating to explore new options to overcome the generalized practice of propofol induction. It is important to administer propofol "slowly" for induction to give the exact amount required for LOC. Regardless of the PK model used for TCI, this technique is also quite helpful because, throughout anesthesia, one knows that

an effect-site concentration of propofol higher than the one required for LOC will contribute to excessive anesthesia.

The absence of a reliable objective method to detect LOC is the main reason for excessive anesthesia or intraoperative awareness. These issues are the basis of motivation to justify the current research project.

1.1 Motivation

The concept of personalized anesthesia requires adjusting the different compounds of general anesthesia to each individual patient. This leads to the need of developing approaches that can provide each patient with the correct hypnotic dose during both induction and maintenance. To accomplish this, one should act correctly on the information available from existing monitors, but also explore new methods capable of filling the known gaps. Because of the currently available DOA monitors, it is possible to assist in the titration of hypnotic drugs during maintenance. However, such monitors are not the best option for the induction of anesthesia, as they have a time delay in processing.

If one accepts that performing propofol induction using a slow-rate infusion offers an advantage, then one faces the question of how to assess the moment of LOC during induction. Currently, in the daily clinical setting, LOC is identified by the loss of response to verbal commands or mechanical stimulus, like tapping on the forehead or squeezing of the shoulder muscles of the individuals. This is because hypnotics have a profound impact on the nerves originating in the brainstem, which disappear during induction and reappear with the recovery of consciousness (ROC), supporting the use of brainstem reflexes as clinical endpoints to assess LOC [6], namely the eyelash, corneal, oculocephalic, gagging and the pupillary light reflexes [7]. While in the daily clinical setting, some anesthesiologists usually assess the eyelash reflex, the assessment of other brainstem reflexes can provide useful insight regarding the actions of hypnotics in the brain and the functional integrity of the different brain regions. However, there are no monitors in place that take advantage of these reflexes to monitor the transition from consciousness to unconsciousness.

The time has come to innovate and to develop new tools to objectively and promptly detect the moment of LOC in the induction phase of general anesthesia. The combination of a slow-rate propofol infusion with the application of a method to detect LOC leaving the patient undisturbed should result in less anesthetic being required and therefore, result in an attenuation of the side effects from overdosing the induction agent, namely arterial hypotension, the most common side effect and a deleterious one, given the evidence that even just 5 minutes of arterial hypotension negatively affect outcome following surgery [8].

The main goal of this project comprised the study and development of a method to objectively and promptly detect the moment of LOC during the transition between consciousness and unconsciousness in the induction phase of general anesthesia in patients subjected to neurosurgeries. This methodology intends to provide an improved means to accurately personalize the concentration of hypnotic in the induction and maintenance for each patient, providing a very unique and attractive solution to anesthesiology worldwide.

1.2 Methodology framework

This study was executed under the doctoral program in Biomedical Engineering from Faculdade de Engenharia da Universidade do Porto (FEUP), supported by an FCT grant with the reference SFRH/BD/98915/2013. The proposed research was conducted at FEUP in collaboration with the anesthesiology research department of Centro Hospitalar e Universitário do Porto (CHUP, Hospital de Santo António). The supervision and support of the research project were accomplished by Professor Joaquim Gabriel Mendes (PhD, FEUP), Pedro Amorim (Medical Doctor expert in anesthesiology at CHUP), and Professor Catarina Nunes (PhD, CHUP, Universidade Aberta).

The CHUP anesthesiology department is a national reference for anesthesia and research. This is clearly evidenced in the many R&D and clinical trials performed by the team over the past 15 years. In addition, there is a rigorous daily clinical practice in the administration of hypnotics and monitoring; therefore, being a reference in anesthesiology and important support for the completion of the current project, which comprises an unestablished research field. Therefore, to limit the variability and assess the suitability of this study, the procedures and technical protocols of CHUP routine clinical practice were preserved and grounded in the standards already established in the field.

To complete a unique and attractive solution that accurately personalizes propofol concentration in the induction and maintenance for each patient, a comprehensive rationale of what hypnotics comprise, and the referring specifications of the methodologies used in routine clinical practice was explored. Based on the assessment of the current methods and principles of the anesthesia practice, to accomplish the personalization of anesthesia, three prominernt consciousness and unconsciousness aspects needed to be carefully addressed: drug administration, monitoring, and feedback (

Figure 1.1).

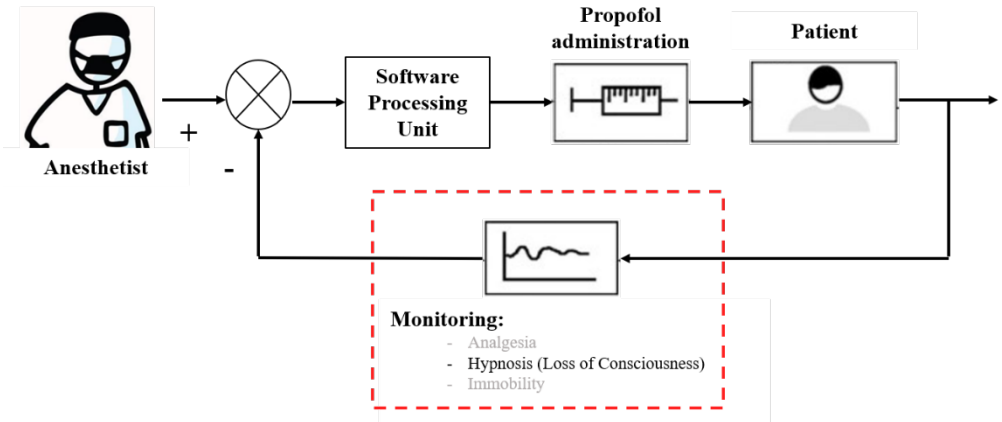


Figure 1.1 General scheme of a system to personalize the propofol concentration by monitoring the three main domains of general anesthesia: analgesia, hypnosis and immobility. In this thesis, the attention was focused on hypnosis because it is where the loss of consciousness occurs.

First, regarding the hypnotic administration, there is considerable variability in everyday clinical practice when hypnotic drugs are used. Frequently, the administration of hypnotics is based on the dosage recommendations of the manufacturers, based on the patient's weight and relying on the experience of trained professionals to individualize the dosage administered, which can vary according to the type and duration of surgery, anesthetic protocol, interaction with other drugs, and others. Propofol is the most commonly used intravenous induction agent for anesthesia providers. It stood out as the hypnotic drug for this study because it is the most used in routine clinical practice due to its advantages over existing anesthetic induction agents including rapid onset and elimination, minimal residual effects on the central nervous system, and decreased incidence of postoperative nausea and vomiting.

Regarding DOA monitoring, due to the currently available monitors, such as the Bispectral Index (BIS) monitor, it is possible to assist in the titration of propofol during maintenance. However, such monitors are not the best option for the induction of anesthesia, as they have a time delay in processing. In agreement with the focus of this research on the achievement of an improved means to accurately personalize the concentration of hypnotic in the induction and maintenance for each patient, it is essential to develop a method to precisely detect LOC during induction of general anesthesia. Currently, in the daily clinical setting, LOC is identified by the loss of response to verbal commands or mechanical stimulus, which is based on subjective analysis. Different solutions were examined and proposed in this thesis to resolve this.

Ultimately, it is essential to combine the propofol delivery and DOA monitoring. One fundamental step is to describe the drug administration over time and relate it with the corresponding effect. Moreover, coupling this information with a feedback control system integrated into a closed-loop approach is the next step to test the performance of the proposed solutions in detecting LOC. However, as it was not the current project's goal, a detailed description in this field is unnecessary. It is important to mention that a closed-loop controller is intended to use the monitoring feedback to adjust the output of a dynamic system and minimize the deviation between the signal and the desired target; therefore, providing an advantageous means to regulate the propofol in the human body.

A set of objectives delineated in the work plan to complete this research project are listed below:

- Understand the usual practice of anesthesiologists in Portugal regarding the administration of propofol during the induction of general anesthesia through a national survey for anesthesiologists' practitioners.
- Review the current state of the knowledge on anesthetic monitoring systems and detect drug-induced loss of consciousness.
- In the context of the basic sciences:
  - Obtain high-quality brain wave recordings during the induction, from patients subjected to general anesthesia with propofol, and explore signal processing techniques and neural networks using these data.
  - Electrically evoke blink reflex during the induction, from patients subjected to general anesthesia with propofol to obtain neurophysiologic-derived parameters of

electromyographic recordings and investigate the existence of differences in the continuum to unconsciousness.

- In the clinical context:
  - Explore the capacity of neural networks to reflect different doses of propofol and different clinically defined levels of responsiveness.
  - Explore the capacity of several electromyographic-derived parameters to reflect the loss of consciousness.
  - Develop an adequate measure for future applications in clinical practice and research with models.
- Ultimately, explore models as solutions for translational research regarding the validation of new surrogates to detect loss of consciousness.

1.3 Relevance and contributions

From the overall project, the benefits of this research can be emphasized. The core contribution of this work is to highlight the importance of detecting the moment a patient subjected to surgery loses consciousness during the induction phase of anesthesia. Moreover, achieving a method to precisely detect that moment brings an advanced patient-specific LOC assessment and a regulation tool for the clinical practice of anesthesiology worldwide. Currently, no such approach is available, allowing the introduction of a new and unique solution to the anesthesiology field.

Some limitations must be considered in terms of the functional characteristics and inherent features of the methodologies that support this research field. Despite these, the success of the proposed technologies, that combines the propofol infusion and detection of loss of consciousness during the induction phase of anesthesia, can critically improve the knowledge in drug-induced loss of consciousness, as well as bringing important benefits to anesthesia by determining the hypnotic amount required for each patient and providing important information to guide the infusion rate required to maintain an adequate level of anesthesia, ensuring a safe and an effective care, reducing the anesthesiologists' workload, and avoiding overdosage or intraoperative awareness.

1.4 List of Publications

This section provides a brief description of the academic publications written during this PhD research. The research done resulted in a number of scientific communications and publications, listed below:

Awards:

- Travel Grant for an Oral Presentation in the Annual Meeting of the American Society of Anesthesiologists (ASA), by FLAD - Luso-American Foundation, 2015.

- Best Poster in the Portuguese Congress of Anesthesiology, by the SPA and Abbvie Pharmaceuticals, 2016.
- SNACC Resident Research Travel Award 44th Annual Meeting, by SNACC Scientific Affairs Committee, 2016.

Publications:

- Ferreira A.L., Nunes C.S., Mendes J.G., Amorim P. "The influence of two different drug infusion profiles on the pharmacodynamics model performance". In: Jaffray D. (eds) World Congress on Medical Physics and Biomedical Engineering, June 7-12, 2015, Toronto, Canada. IFMBE Proceedings, vol 51. Springer, Cham. doi:10.1007/978-3-319-19387-8_214.
- Ferreira A.L., Mendes J., Amorim P., Nunes C.S. (2018). EEG signatures at the transition between conscious and unconscious state during induction of general anesthesia with remifentanil and propofol. IEEE International Symposium on Medical Measurements and Applications (MeMeA), Rome, 2018, pp. 218-222. https://doi.org/10.1109/MeMeA.2018.8438635
- Ferreira A.L., Mendes J., Amorim P., Nunes C.S. (2018). Neuro-fuzzy models to predict the required propofol amount for loss of consciousness during general anesthesia: a preliminary study. IEEE International Symposium on Medical Measurements and Applications (MeMeA), Rome, 2018, pp. 587-591, https://doi.org/10.1109/MeMeA.2018.8438635
- Ferreira A.L., Nunes C., Mendes J.G., Amorim P. (2019). Do we have today a reliable method to detect the moment of loss of consciousness during induction of general anaesthesia?. Revista Espanola de Anestesiologia y Reanimacion, 66(2), 93–103. https://doi.org/10.1016/j.redar.2018.06.008
- Ferreira A.L., Mendes J.G., Nunes C.S., Amorim P. (2019). Evaluation of Bispectral Index time delay in response to anesthesia induction: an observational study. Brazilian Journal of Anesthesiology, 69(4), 377–382. https://doi.org/10.1016/j.bjan.2019.03.008
- Ferreira A.L., Correia R., Vide S., Ferreira A.D., Kelz M.B., Mendes J.G., Nunes C.S., Amorim P. (2020). Patterns of Hysteresis Between Induction and Emergence of Neuroanesthesia Are Present in Spinal and Intracranial Surgeries. Journal of Neurosurgical Anesthesiology, 32(1), 82–89. https://doi.org/10.1097/ANA.0000000000000559
- Ferreira A., Vide S., Felgueiras J., Cardoso M., Nunes C., Mendes J.G., Amorim P. (2020). Electromyographic assessment of blink reflex throughout the transition from responsiveness to unresponsiveness during induction with propofol and remifentanil. Journal of Clinical Monitoring and Computing. https://doi.org/10.1007/s10877-020-00593-w
- Ferreira A.L., Mendes J., Nunes C., Amorim P. (2020). Propofol administration in the induction phase of general anesthesia in Portugal. Revista Da Sociedade Portuguesa De Anestesiologia, 29(1), 6 - 11. https://doi.org/10.25751/rspa.18834
- Ferreira A., Nunes C.S., Vide S., Felgueiras J., Cardoso M., Amorim P., Mendes J.G. (2020). Performance of blink reflex in patients during anesthesia induction with propofol and

remifentanil: Prediction Probabilities and Multinomial Logistic Analysis. BioMedical Engineering OnLine, 19(84). https://doi.org/10.1186/s12938-020-00828-6

- Ferreira A.L., Vide S., Nunes C., Neto J., Amorim P., Mendes J. (2021). Implementation of neural networks to frontal electroencephalography for the identification of the transition responsiveness/unresponsiveness during induction of general anesthesia. IRBM Innovation and Research in BioMedical engineering. https://doi.org/10.1016/j.irbm.2021.02.004

Communications:

Abstracts of scientific communications presented in international conferences are listed here. Most were published in supplements of the European Journal of Anaesthesiology, and the Journal of Neurosurgical Anesthesiology.

- Ferreira A.L., Nunes C., Rato A., Mendes M., Amorim P. (2015). Using the calculated propofol concentration at loss of consciousness at the post-induction target for TCI anesthesia, results in a significant decrease in BIS and blood pressure independently of the PK model. Abstracts From the 43rd Annual Meeting of the Society for Neuroscience in Anesthesiology and Critical Care, San Diego, CA, October 23, 2015, Journal of Neurosurgical Anesthesiology, 27(4), 430-431. https://doi.org/10.1097/ANA.0000000000000217
- Ferreira A.L., Castro A., Pedrosa S., Gabriel J., Amorim P. (2015). Anesthesia induction with propofol and remifentanil for neurosurgery: identification of a BIS time delay. Abstracts From the 43rd Annual Meeting of the Society for Neuroscience in Anesthesiology and Critical Care, San Diego, CA, October 23, 2015, Journal of Neurosurgical Anesthesiology, 27(4), 432-433. https://doi.org/10.1097/ANA.0000000000000217
- Ferreira A.L., Nunes C., Gabriel J., Lobo F., Amorim P. (2015). A survey on the practice of anesthesia induction and loss of consciousness assessment. Abstracts From the 43rd Annual Meeting of the Society for Neuroscience in Anesthesiology and Critical Care, San Diego, CA, October 23, 2015, Journal of Neurosurgical Anesthesiology, 27(4), 452-453. https://doi.org/10.1097/ANA.0000000000000217
- Ferreira A.L., Nunes C., Tedim A., Castro A., Pedrosa S., Amorim P. (2015). Efficacy of a new method to administer propofol aiming maintaining the BIS between 60 and 40 throughout the induction phase. Abstracts From the 43rd Annual Meeting of the Society for Neuroscience in Anesthesiology and Critical Care, San Diego, CA, October 23, 2015, Journal of Neurosurgical Anesthesiology, 27(4), 460. https://doi.org/10.1097/ANA.0000000000000217
- Ferreira A., Nunes C., Castro A., Ferreira A.L., Pedrosa S., Amorim P. (2015). A high variability in propofol requirements for anesthesia induction is shown independently of remifentanil. Abstracts From the 43rd Annual Meeting of the Society for Neuroscience in Anesthesiology and Critical Care, San Diego, CA, October 23, 2015, Journal of Neurosurgical Anesthesiology, 27(4), 431- 432. https://doi.org/10.1097/ANA.0000000000000217

- Ferreira A., Nunes C., Tedim A., Cunha M., Ferreira A.L., Amorim P. (2015). Inter-patient variability and predictive factors of propofol requirements and estimated concentrations for loss of consciousness and recovery. Abstracts From the 43rd Annual Meeting of the Society for Neuroscience in Anesthesiology and Critical Care, San Diego, CA, October 23, 2015, Journal of Neurosurgical Anesthesiology, 27(4), 460-461.
  https://doi.org/10.1097/ANA.0000000000000217
- Cordeiro L., Ferraz S., Duque M., Ferreira A., Ferreira A.L., Amorim P. (2015). Bispectral index and spectral edge frequency may have a clinically relevant processing time delay, unrelated to the smoothing rate set on the BIS monitor. Abstracts From the 43rd Annual Meeting of the Society for Neuroscience in Anesthesiology and Critical Care, San Diego, CA, October 23, 2015, Journal of Neurosurgical Anesthesiology, 27(4), 464-465.
  https://doi.org/10.1097/ANA.0000000000000217
- Duque M., Amorim P., Ferreira A.L., Costa D., Ferreira A. (2015). The bispectral index (BIS) may have a clinically significant processing time delay that may be independent of the smoothing rate (SR). Euroanaesthesia 2015: The European Anaesthesiology Congress, Berlin, Germany, 30 May – 2 June, 2015, European Journal of Anaesthesiology, 32(53), 12-13.
- Ferreira A.L., Correia R., Nunes C.S., Amorim P. (2016). Survey: how much and how to administer propofol in the induction phase of general anesthesia and how to evaluate its effects. Euroanaesthesia 2016: The European Anaesthesiology Congress, London, United Kingdom, 28-30 May, 2016, European Journal of Anaesthesiology, 33(54), 89-90.
- Ferreira A.L., Correia R., Santos F., Ferreira A., Nunes C.S., Amorim P. (2016). Comparison between methods of anesthesia induction using a combination of TCI and constant infusion rates. Euroanaesthesia 2016: The European Anaesthesiology Congress, London, United Kingdom, 28-30 May, 2016, European Journal of Anaesthesiology, 33(54), 90.
- Ferreira A.L., Nunes C.S., Ferreira A., Correia R., Vide S., Amorim P. (2016). Hysteresis observed in the onset and offset of propofol-induced unconsciousness in surgical patients suggests that neural inertia exists in humans. Euroanaesthesia 2016: The European Anaesthesiology Congress, London, United Kingdom, 28-30 May, 2016, European Journal of Anaesthesiology, 33(54), 213.
- Ferreira A., Ferreira A.L., Nunes C.S., Correia R., Amorim P. (2016), Inter-patient variability of propofol requirements for anesthesia. Euroanaesthesia 2016: The European Anaesthesiology Congress, London, United Kingdom, 28-30 May, 2016, European Journal of Anaesthesiology, 33(54), 226.
- Ferreira A.L., Nunes C.S., Ferreira A., Vide S., Correia R., Amorim P. (2016). Hysteresis at loss and return of consciousness with propofol anesthesia in surgical patients may be evidence of neural inertia in humans. Abstracts From the 44th Annual Meeting of the Society for Neuroscience in Anesthesiology and Critical Care, Chicago, IL, October 20- 21, 2016, Journal of Neurosurgical Anesthesiology, 28(4), 471-472.

https://doi.org/10.1097/ANA.0000000000000358

- Vide S., Correia R., Ferreira A.L., Ferreira A., Nunes C.S., Amorim P. (2016). Individualizing propofol target controlled infusion (TCI) anesthesia: an addition to depth of anesthesia monitors in an attempt to prevent awareness? Abstracts From the 44th Annual Meeting of the Society for Neuroscience in Anesthesiology and Critical Care, Chicago, IL, October 20- 21, 2016, Journal of Neurosurgical Anesthesiology, 28(4), 478.
  https://doi.org/10.1097/ANA.0000000000000358
- Ferreira A., Ferreira A.L., Cunha M., Correia R., Nunes C.S., Amorim P. (2016). Wide inter-patient variability in metabolism measured by indirect calorimetry during general anesthesia and surgery does not influence propofol requirements. Abstracts From the 44th Annual Meeting of the Society for Neuroscience in Anesthesiology and Critical Care, Chicago, IL, October 20-21, 2016, Journal of Neurosurgical Anesthesiology, 28(4), 496.
  https://doi.org/10.1097/ANA.0000000000000358
- Ferreira A.L., Nunes C.S., Lobo F., Mendes J., Amorim P. (2016). How expert anesthesiologists perform and understand propofol induction: results from a survey. Abstracts From the 44th Annual Meeting of the Society for Neuroscience in Anesthesiology and Critical Care, Chicago, IL, October 20-21, 2016, Journal of Neurosurgical Anesthesiology, 28(4), 505- 506. https://doi.org/10.1097/ANA.0000000000000358.
- Ferreira A.L., Correia R., Nunes C.S., Vide S., Ferreira A., Amorim P. (2016). Calculated overshoot in propofol cerebral concentration at induction showed no correlation in the observed fall in BIS or systolic pressure. Abstracts From the 44th Annual Meeting of the Society for Neuroscience in Anesthesiology and Critical Care, Chicago, IL, October 20- 21, 2016, Journal of Neurosurgical Anesthesiology, 28(4), 451-452.
  https://doi.org/10.1097/ANA.0000000000000358
- Ferreira A.L., Nunes C.S., Amorim P., Ferreira A., Vide S., Correia R. (2016). Individual effect-site concentrations of propofol at return and loss of consciousness are correlated. 9th International Update on Neuroanesthesia and Neurointensive Care EURONEURO 2016, Journal of Neurosurgical Anesthesiology, 28(2), 8. https://doi.org/10.1097/ANA.0000000000000287
- Ferreira A., Vide S., Correia R., Nunes C., Amorim P. (2017). Predicting loss of consciousness using the pupillary light reflex. Abstracts from the 45th Annual Meeting of the Society for Neuroscience in Anesthesiology and Critical Care, Boston, MA, October 19–20, 2017, Journal of Neurosurgical Anesthesiology: 29(4), 555-556.
  https://doi.org/10.1097/ANA.0000000000000452
- Nunes C., Ferreira A.L., Correia R., Amorim P. (2017). Towards personalized anesthesia: predictive factors for propofol requirements for loss of consciousness. Abstracts from the 45th Annual Meeting of the Society for Neuroscience in Anesthesiology and Critical Care, Boston, MA, October 19– 20, 2017, Journal of Neurosurgical Anesthesiology: 29(4), 563-564 https://doi.org/10.1097/ANA.0000000000000452

- Ferreira A.L., Nunes C., Mendes J., Amorim P. (2018). Transition to loss of consciousness during anesthesia induction with remifentanil and propofol: EEG patterns. Abstracts from the 46th Annual Meeting of the Society for Neuroscience in Anesthesiology and Critical Care, San Francisco, CA, October 11-12, 2018, Journal of Neurosurgical Anesthesiology: 31(4), 481- 482. https://doi.org/ 10.1097/ANA.0000000000000531
- Ferreira A., Nunes C., Felgueiras J., Cardoso M., Mendes J., Amorim P. (2019). The blink reflex as a useful approach for assessing the effect of propofol during the induction phase of anesthesia. Abstracts from the 47th Annual Meeting of the Society for Neuroscience in Anesthesiology and Critical Care, Phoenix, AZ, September 12-14, 2019, Journal of Neurosurgical Anesthesiology: 31(4), 481-482. https://doi.org/10.1097/ANA.0000000000000630

Publications Undergoing Review:

- Vide S., Ferreira A.L., Kreuzer M., Couto M., Agustí M., Chen A., Jaramillo S., Schneider G., García P., Amorim P., Trocóniz I., Larson M., Gambús P., Cortical, brainstem and autonomic responses to nociception under total intravenous anesthesia with propofol and remifentanil, Anesthesia & Analgesia.
- Linassi F., Vide S., Ferreira A.L., Schneider G., Gambús P., Kreuzer M., Relationships between the qNOX, qCON, burst suppression ratio, and muscle activity index of the CONOX monitor, British Journal of Anaesthesia.

1.5 Thesis Outline

The outline of this thesis is presented below, which provides a binding version across the contents and contributions of the conducted research.

This thesis is divided into seven main chapters, as follows:

Chapter 1 – INTRODUCTION. In the present chapter, a brief background statement and motivation of the work are included, as well as an overview of the investigation scope on the monitoring of hypnosis. Then, a methodological framework is included to justify the approach being pursued in the execution of the work. The research objectives are presented, followed by a brief description of the main contributions of the project. At last, a list of the academic publications accomplished in the completion of this project is summarized.

Chapter 2 – LITERATURE REVIEW. In this chapter, background information on the anesthesia practice is performed, describing the fundamental aspects of the hypnosis approaches and DOA monitoring techniques used in clinical practice. Furthermore, a questionnaire survey was conducted to assess the usual practice of anesthesiologists in Portugal on how they administer propofol in the induction phase of GA and how they evaluate its effects. Another review was completed to give an overview of the current methods to monitor DOA and detect LOC.

Chapter 3 – PROPOFOL REQUIREMENTS AT LOSS OF CONSCIOUSNESS. The present chapter starts by presenting a retrospective study performed to evaluate the inter-patient variability of the amount of propofol required for LOC. Inter-patient variability was assessed and quantified, and some predictive factors were identified. Then are presented the results of a preliminary study with a neuro-fuzzy model used to predict the amount of propofol required for LOC.

Chapter 4 – PATTERNS OF HYSTERESIS BETWEEN INDUCTION AND EMERGENCE OF NEUROANESTHESIA. In this chapter is presented a study conducted to discuss the existence of neural inertia, which is the observed resistance to changes in consciousness induced by general anesthesia, independent of drug kinetics, the conceptual and practical impact, this phenomenon may have in induction and recovery from general anesthesia.

Chapter 5 – ELECTROENCEPHALOGRAPHY IN THE DETECTION OF LOSS OS CONSCIOUSNESS. Acknowledging that there is wide inter-patient variability in propofol requirements for LOC as well as the existence of hysteresis between propofol concentrations at LOC and Recovery of Consciousness (ROC), results in important evidence of the need to implement methods to personalize medicine to anesthesiology. Therefore, and because personalized anesthesia involves the precise detection of the moment of LOC during the continuum to unconsciousness, in this chapter, the electroencephalographic (EEG) signatures associated with the moment of LOC are examined as a starting point to create a robust model for tracking the dynamic changes between conscious and unconscious state. Using the information provided by this study, a neural network model was applied to the EEG signals recorded from the BIS monitor during neurosurgical procedures, and the performance of the model in detecting, with precision, the transition between no-LOC and LOC was evaluated.

Chapter 6 – ELECTROMYOGRAPHY IN THE DETECTION OF LOSS OF CONSCIOUSNESS. In this chapter, neurophysiologic-derived parameters of EMG records of the electrically evoked blink reflexes are studied to evaluate their use in identifying LOC. From the EMG records of electrically evoked blink reflexes, different electromyogram features were extracted and compared. The ability of these features to distinguish between LOC and no-LOC was assessed using prediction probability analysis and multinomial logistic regression models. The results are presented in this chapter, as it is the main chapter of this work.

Chapter 7 – CONCLUSIONS AND FUTURE WORK. This chapter has the purpose of presenting the overall conclusions of this research project, emphasizing the main contributions of the work. Also, are summarized the implications of the findings and the recommendations for future investigation.

At the end of this document, three sets of appendixes are presented. The first is the questionnaire developed and sent to the Portuguese anesthesiologists and used for the work presented in Chapter 2. The second is the clinical protocol, informed consent form, and acceptance letter used for the study regarding the propofol requirements at the loss of consciousness presented in Chapter 3. And the third set of appendixes is the clinical protocol, informed consent form, and acceptance letter used for the studies with electromyography, presented in Chapter 6.

2 LITERATURE REVIEW

This chapter is divided into two main sections, section 2.1 is a survey on the usual practice of anesthesiologists in Portugal regarding the administration of propofol during the induction of general anesthesia. Section 2.2 is a global overview of the existing methods to detect the moment of loss of consciousness during the induction of general anesthesia.

The study described in the first section led to a published paper in the Revista Portuguesa de Anestesiologia, an abstract presented at the 43rd SNACC Annual Meeting 2015 and an abstract presented at American Society of Anesthesiologists Annual Meeting (ASA) 2015:

i. Propofol Administration in the Induction Phase of General Anesthesia in Portugal, Revista da Sociedade Portuguesa de Anestesiologia, 2020; Volume 29; Number 1.
ii. A survey on the practice of anesthesia induction, presented at ASA 2015, 24-28 October, San Diego, California.
iii. A survey on the practice of anesthesia induction and loss of consciousness assessment, Journal of Neurosurgical Anesthesiology 2015, Volume 27, Number 4.

The study presented in the second section led to a published paper in the Revista Española de Anestesiología y Reanimación:

i. Do we have today a reliable method to detect the moment of loss of consciousness during induction of general anesthesia?, Revista Española de Anestesiología y Reanimación, 2019 Feb; 66(2); 93-103.

This chapter is organized as follows:

2.1 Propofol administration in the induction phase of general anesthesia in Portugal.
2.2 Overview of the current methods to monitor the depth of anesthesia and detect loss of consciousness.

2.1 Propofol administration in the induction phase of general anesthesia in Portugal

Ana Leitão Ferreira MSc, Joaquim Gabriel Mendes PhD, Catarina Nunes PhD, Pedro Amorim MD

Abstract

Introduction: Administering propofol intravenously adequately during induction of general anesthesia implies a good knowledge of pharmacokinetics and pharmacodynamics, a good understanding of how anesthesia alters consciousness and the ability to correctly interpret vital signs monitoring. The purpose of this study was to assess the usual practice of anesthesiologists in Portugal regarding the administration of propofol during the induction of general anesthesia.

Methods: A transversal observational analytical and descriptive study, conducted through a questionnaire sent by e-mail to all anesthesiologists of several Portuguese hospitals. The questionnaire presented a conventional scenario (male subject, 50 years, 60 kg, 160 cm, American Society of Anesthesiologists (ASA) I, submitted to general anesthesia with 1% propofol) and has 10 questions directed to the administration of propofol during induction phase of general anesthesia. A descriptive analysis of the data was performed through SPSS 23.0®.

Results: A total of 118 physicians responded to the survey, most of whom were experts for more than 5 years (56.9%). Based on the presented scenario, most anesthesiologists would administer a propofol dose of 60 mg at induction, at a rate greater than 1200 mL/h, and would assess loss of consciousness by evaluating loss of the eyelid reflex, which, in BIS index, would be reflected in a 60 value. Most participants measure the patient's blood pressure every 5 minutes and have never used target-controlled infusion systems.

Discussion: The survey showed that there is a wide variety of methods to assess the loss of consciousness, a diversity in handling propofol in induction, a lack of experience in the use of target-controlled infusion systems and in the evaluation of the relationship between dose, velocity and concentration of propofol. In this work, some suggestions were also made for anesthesiologists to consider implementing in their clinical practices.

Conclusion: There seems to be a diversity in the amount and in the way propofol is used by the Portuguese anesthesiologists to induce general anesthesia.

Keywords: Anesthesiologists; Surveys and Questionnaires; Propofol; Induction; General Anesthesia.

Introduction

According to the Central Administration of the Health System in Portugal, more than 600 000 patients have been submitted to surgery in 2016 [9]. As the population is aging, and more people have access to medical services, it is expected that this number will increase in the future. In 2015, there were 1280 anesthesiologists and about 300 interns working at the public hospital in Portugal [10].

At its core, general anesthesia can be divided into induction, maintenance, and recovery. Regarding induction, it is a crucial stage, since one seeks to stabilize the patient for the remainder of the surgery. A proper induction of general anesthesia can prevent or reduce two main serious problems: awareness and overdosing.

Awareness is characterized by the patient being awake during surgery. Awareness events are reported to occur in about 2 out of 1000 surgeries with general anesthesia in the United States of America [11]. This occurrence can create deep psychological consequences in the patient and can also generate heart conditions, such as ischemia and infarction or adverse reactions to different combinations of drugs. A long post-operatory recovery is also associated with this intraoperative awakening.

Overdosing may be the consequence of an overshooting, which is a phenomenon that occurs due to another relevant characteristic known as hysteresis [12]. Hysteresis is the time delay between the peak of plasma concentration and the peak of the effect-site concentration. This leads to a continuous increase of the effect-site concentration even after the infusion is stopped. The difference between the maximum value of effect-site concentration and the effective LOC effect-site concentration is then described as overshoot. The magnitude of the overshoot and hysteresis depends on the pharmacokinetic model.

Propofol is the most commonly used intravenous anesthetic agent for the induction of general anesthesia [13]. During induction with propofol, the moment at which the patient loses consciousness is of extreme importance to determine the concentration required for a particular individual and it is critical to the accurate tuning of the depth of anesthesia. In fact, there is currently no effective and automatic mechanism for the determination of LOC. Consequently, the existence of these uncertainties leads to mistakes or accidents that may endanger human lives. Precise and timed monitoring of the patient's response to the anesthetic drugs is therefore a crucial task to help clinicians to titrate anesthesia to match individual patient needs.

The purpose of this work is to assess the usual practice of anesthesiologists in Portugal regarding the administration of propofol during the induction of general anesthesia.

Materials and Methods

Transversal observational analytical and descriptive study directed at internal doctors with specific training and specialists in Anesthesiology working in the main public hospitals in Portugal, from December 2014 to April 2015.

A questionnaire was designed with the help of an experienced anesthesiologist to guarantee a proper context and to avoid bias. The questionnaire, comprising 10 questions about the administration of propofol in the induction phase of general anesthesia, was implemented using Google Drive and was sent by the Secretariat of the Anesthesiology Service of the Centro Hospitalar do Porto to the department directors that forwarded to all their anesthesiologists. The questionnaire was then sent to the following Hospitals: Centro Hospitalar do Porto, Centro Hospitalar de São João, Centro Hospitalar de Gaia-Espinho, Centro Hospitalar de Trás-os-Montes e Alto Douro, Centro Hospitalar e Universitário de Coimbra, and Centro Hospitalar de Lisboa Central.

The questionnaire was intended to take about five minutes to respond to. It was anonymous and was used for research purposes only. There was no way to identify the clinician's department which responded. The questionnaire was not a test, because there were no correct or incorrect answers.

Before the questions, the anesthesiologists were presented with a scenario for them to consider and analyze. The scenario was as follows: "A male patient (50 years, 60 kg, 160 cm, ASA physical state I) without premedication, undergoing general anesthesia and tracheal intubation for laparotomy procedure to perform a cholecystectomy. Three minutes before induction, 0.15mg of fentanyl was administered. General anesthesia was induced with 1% propofol by a 20cc syringe. The anesthesiologist was at the bedside pre-oxygenating, monitoring, and instructing the nurse who administers the drugs through an intravenous line inserted in the back of the patient's hand. ASA and BIS were standard monitoring."

The complete survey is presented in Appendix A.

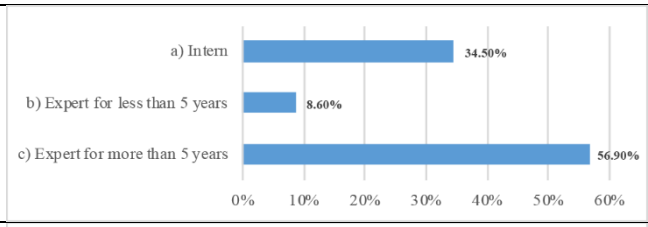
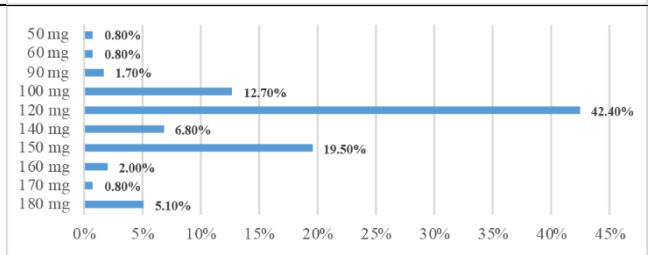
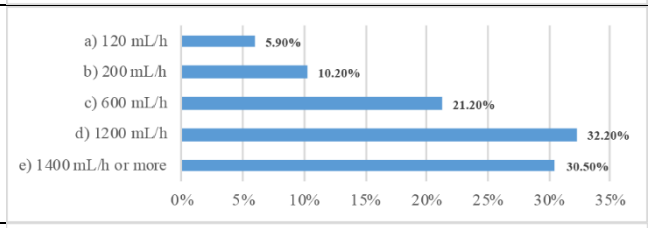
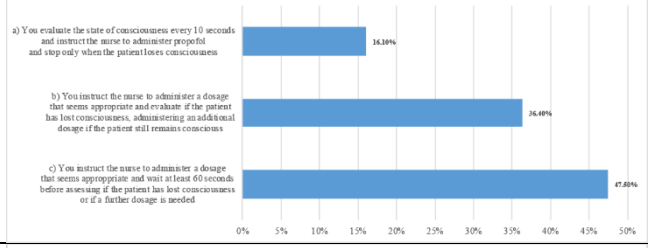
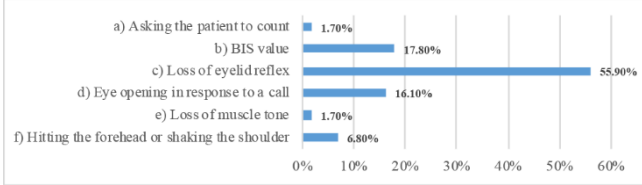
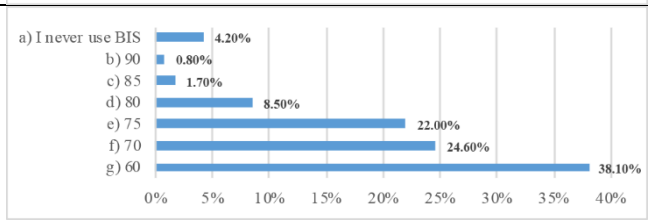
The answers were collected and organized in Statistical Package for the Social Sciences (SPSS 23.0®) software for subsequent analysis. Descriptive statistics, namely frequencies, were used to describe the basic characteristics of the answers. Non-parametric tests were used during analyses since the data was not normally distributed. Spearman correlation coefficient was used to analyze the correlation between the answers given by the anesthesiologists (variables). The Chi-square of independence was used to test for a statistically significant relationship between the variables. The statistical significance was considered for $p\text{-value} < 0.05$. Results are presented in frequency tables, bar graphs, or pie charts, in the next section.

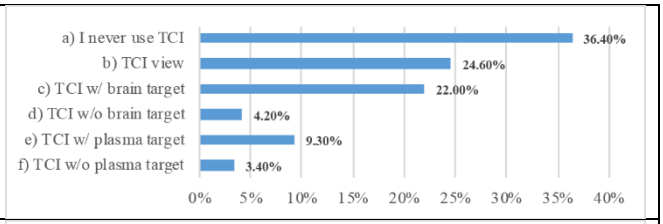
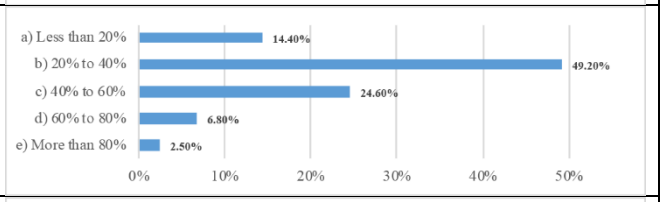
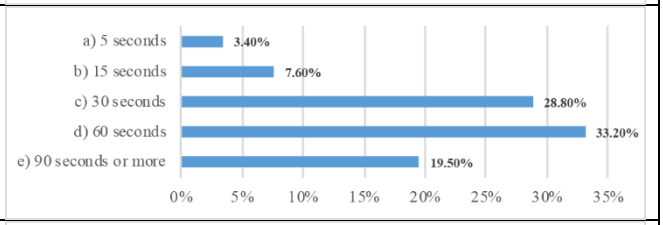
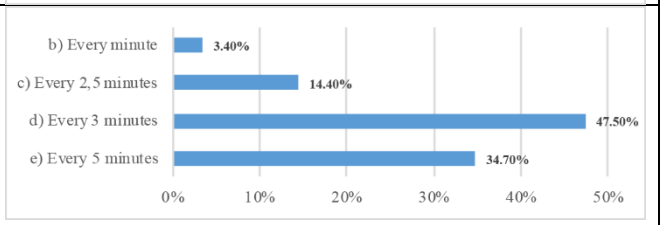
Results

One-hundred ten (110) physicians answered the questionnaire: about 63 experts in anesthesiology for over 5 years, 38 interns, and 9 experts for less than 5 years.

The distribution of the answers to all questions, based on the scenario presented in the Materials and Methods section, is presented in Table 2.1.

Table 2.1 Distribution of the answers to all questions in the questionnaire.

1. What is your experience as an anesthesiologist?	
2. What dosage of propofol would you administer for induction?	
3. In your clinical practice, for the chosen dosage, how fast would the administration of propofol (1% by a 20cc syringe administered by a nurse) typically be performed?	
4. When performing the induction, with an administration of propofol with the dosage and speed set, how would you proceed?	
5. During the induction of anesthesia with propofol, which method would you use to assess loss of consciousness?	
6. When you monitor the patient with BIS and the index would start to decrease during induction as a result of propofol administration, what would be the value below which you can tell when patients, on average, lose consciousness?	

7. When you use propofol TCI with the Schnider model, how would you perform induction, in most cases?	
8. Overshooting occurs during induction, when you stop administering propofol. Considering the scenario presented, what would be the magnitude of the overshoot?	
9. How long after the injection will the concentration of propofol in the brain achieve its maximum?	
10. During the administration of anesthesia and using a non-invasive method, how often would you measure blood pressure for an ASA I, 50 years old, 60 kg and 160 cm patient?	

In question 1 was asked what dose of propofol would be administered for induction by the anesthesiologist, given the scenario presented, and the majority of participants (42.4%) answered that they would administer 120 mg of propofol. With regard to the dose chosen in question 1, the participant was asked to choose the infusion velocity of propofol from the following options: 120ml/h, 200ml/h, 600ml/h, 1200ml/h, or 1400ml/h or more. Only 19 anesthesiologists (16.1%) chose a rate of infusion below 200 mL/h, which can be considered a slow infusion. Regarding the question on the anesthesiologist's protocol while performing induction, the answer "Instructing the nurse to administer a dosage that seemed appropriate and evaluate if the patient had lost consciousness, and administering an additional dosage if the patient remained conscious" was the most selected by the participants (n=56). Thirty-six percent (36%) of the participants answered that they would instruct the nurse to administer a dosage that seemed appropriate and would wait at least 60 seconds before assessing if the patient had lost consciousness or if a further dosage was needed. And, 19 anesthesiologists would prefer to evaluate the state of consciousness every 10 seconds and would instruct the nurse to administrate propofol and stop only when the patient loses consciousness. When asked which method they would use to assess the loss of consciousness during induction of propofol, most anesthesiologists (53.4%) would assess the loss of consciousness by evaluating

loss of eyelid reflex. Twenty-three participants (19.5%) would assess LOC by relying on the BIS value, and 14 (11.9%) would observe the absence of eye-opening or movement in response to call. Twelve anesthesiologists (10.2%) would consider the absence of any movement when hitting the forehead or shaking the patient's shoulder as the most important method to evaluating LOC, and only three (2.5%) would ask the patient to count (up to ten or twenty, for example), and would consider that LOC occurs when the patient stops counting or stops reacting (no movement) in response to a pinch in the shoulder. The participants could write their responses in an empty box if they would use an approach other than the one selected in the previous question. Eight participants would also rely on the BIS value, 3 on the loss of eyelid reflex, and 5 or on the absence of movement to evaluate the loss of consciousness during induction with propofol. Regarding the question: "Which is the value below which you can tell when a patient loses consciousness, on average, when monitoring with BIS?", the majority of the anesthesiologists (38.2%) would consider a value of 60 in BIS for LOC. When asked about the use of propofol TCI of propofol with the Schnider's model [14], 24.6% would use it only on TCI-View mode and 39% would use pre-determined TCI mode. About thirty-six per cent (36.4%) of the participants never used TCI systems. Considering the scenario presented, the dosage and the rate of administration selected in the previous answers, anesthesiologists were asked about the estimated magnitude of the overshoot when propofol administration was stopped, and, most participants (n=87) referred to 20% to 60%. For a patient with the characteristics described in the scenario presented, question 9 asked: "How long after the end of the bolus of propofol will the patient achieve its maximum brain concentration (when performing the induction with 3µg/kg of fentanyl and a propofol bolus of 100mg administered over 30 seconds)?". Most anesthesiologists referred to 60 seconds (39%) or 30 seconds (28.8%). Regarding the last question, participants were asked how often they would measure the blood pressure (using a non-invasive method) during the anesthetic procedure. Most anesthesiologists (47.5%) would measure blood pressure every 5 minutes, 34.7% would measure it every 3 minutes, 14.4% every 2.5 minutes, and 43.4% would continuously measure it.

It was considered 9 different variables, corresponding to the last 9 questions of the questionnaire, which can be measured accordingly to different types such as scale, ordinal or nominal - experience as an anesthesiologist (nominal), dose (scale), velocity (ordinal), procedure (nominal), LOC assessment (nominal), BIS value at LOC (ordinal), TCI (nominal), overshoot (nominal), time to maximum brain concentration (ordinal) and time measuring blood pressure (nominal).

According to the Spearman rank correlation coefficient analysis, results showed a significant association between the velocity of propofol chosen by the participants for administering propofol and the method they used to determine LOC. It was also found a significant correlation between time measuring blood pressure and the experience as an anesthesiologist.

Table 2.2 shows the results for the Pearson Chi-Square test considering the categorical (nominal and ordinal) variables. The following variables have a statistically significant relationship:: infusion velocity and LOC assessment ($p=0.018$); infusion velocity and BIS value at LOC ($p=0.033$); infusion velocity and time to maximum brain concentration ($p=0.016$); BIS value at LOC and time to maximum brain concentration ($p=0.034$); and, time to maximum brain concentration and time measuring blood pressure ($p=0.020$). The results of the Kruskal-Wallis 1-way analysis of variance (ANOVA) test show no relations between the dose (scale variable) and the other variables ($p>0.05$).

Discussion

This study reports on the results from a survey developed to assess the usual practice of anesthesiologists in Portugal, concerning the administration of propofol, intravenously, for induction of general anesthesia.

Participation in this study was not what would be desirable in terms of the number of responses: only 8% of the Portuguese anesthesiologists responded. It was not clear whether the low adherence to the study was the result of demotivating professionals or the inefficiency of the medium chosen for the dissemination of questionnaires; for example, some emails not active, incorrect, directly sent to spam or colleagues did not have an available email.

The anesthetic induction dose of propofol in adults varies from 2.0 to 2.5 mg/kg with recommended maintenance infusion rates ranging from 0.05 to 0.2 mg/kg/min, depending on the depth of anesthesia that is required [15]. This means that in the induction phase of the scenario presented in the questionnaire, in which a male patient weighs 60 kg, the recommended dose of propofol should be between 120 and 150 mg. In clinical practice and according to the results of the survey, most anesthesiologists would administer a dose that ranged between 100 mg and 150 mg.

Table 2.2 P-values for the Pearson Chi-Square test relating the different questions of the survey.

Questions about	Infusion Velocity	Procedure	LOC assessment	BIS value at LOC	TCI	Overshoot	Time to maximum brain concentration	Time measuring blood pressure	Experience as anesthesiologist
Infusion Velocity	-	0.099	0.018*	0.033*	0.421	0.149	0.016*	0.123	0.195
Procedure	0.009	-	0.382	0.678	0.445	0.304	0.897	0.691	0.549
LOC assessment	0.018*	0.382	-	0.030	0.935	0.427	0.395	0.081	0.361
BIS value at LOC	0.033*	0.678	0.030	-	0.080	0.615	0.034*	0.368	0.677
TCI	0.421	0.445	0.935	0.08	-	0.684	0.432	0.362	0.085
Overshoot	0.149	0.304	0.427	0.615	0.684	-	0.634	0.710	0.496
Time to maximum brain concentration	0.016*	0.897	0.395	0.034*	0.432	0.634	-	0.020*	0.539
Time measuring blood pressure	0.123	0.691	0.081	0.368	0.362	0.71	0.020*	-	0.147
Experience as anesthesiologist	0.195	0.549	0.361	0.677	0.085	0.496	0.539	0.147	-

*p<0.05.

Apparently, anesthesiologists are following the recommendations. When asked about the infusion rate for administering the dose of propofol in induction, only slightly above 50% of the anesthesiologists would choose 1200 ml/h or more. An infusion of about 120 mg takes up to 40 seconds to be completed, which means that the infusion rate needed to be performed at, at least, 1000 mL/h.

The determination of an adequate infusion rate and a proper dose of propofol proved already to restrict the overshoot during induction. Studies have shown that the expected doses for anesthesia onset are affected by changes in the injection rate [16][17]. Another study showed that the propofol dose is reduced by using slower infusion rates, while rapid infusion rates have resulted in greater decreases in heart rate and a higher incidence of apnea [18]. A slow infusion rate results in a longer duration of induction but requires a lower dose of propofol, which decreases blood pressure and incidence of apnea [19].

As demonstrated in a previous study [20], the amount of propofol required to produce unconscious varies widely from patient to patient and was independent of age, gender, weight, or height. It has been shown that there is no way to predict how much propofol an individual patient will need. The suggestion is that anesthesiologists replace the recommendation of administering a specific amount of propofol based on patient weight and age with a technique that enables individualization of a patient's needs, i.e. administering propofol slowly at induction.

Regarding the monitoring of the patient during induction, approximately 50% of the participants would administer a dose of propofol that seems appropriate to the patient and evaluate if the patients have lost consciousness, administering an additional dosage if the patient remains conscious. In this matter, only 16% of the anesthesiologists would evaluate the state of consciousness every 10 seconds and would administer propofol until the patient loses consciousness, stopping the administration of propofol at this time. When asked which method the anesthesiologists would use to determine if the patient was unconscious during the administration of propofol, the responses vary widely: some anesthesiologists would rely on loss of eyelid reflex, others on BIS value, others on the observation of the absence of eye-opening or movement in response to call, absence of any movement when hitting the forehead or shaking the patient's shoulder and some anesthesiologists would ask the patient to count. This shows the uncertainty regarding the method that should be used to ensure a correct assessment of the dose of propofol during induction of general anesthesia.

It is suggested that, in addition to slowly infusing propofol during induction, anesthesiologists should monitor the response of the patient to a stimulus, every 10 seconds, to precisely assess the moment of loss

of consciousness, thus identifying the amount of propofol each patient needs. And then use that information to guide the infusion rate of propofol required to maintain an adequate level of anesthesia. The question now is on which method would be better for monitoring patient's responses every 10 seconds.

To avoid complications, such as awareness [11][21] or excessive anesthesia, the anesthesiologists should be aware of situations that cause false BIS readings. In this study, most anesthesiologists had the perception that the magnitude of the overshooting, in the scenario presented, was from 20 to 60%. According to the t-test for paired samples, there was a correlation between the velocity chosen in the administration of propofol and the magnitude of the overshooting. This means that the anesthesiologists were sensitive to the occurrence of this phenomenon at a pharmacodynamic level. The familiarity of this behavior is important since overdosing is associated with the increase of morbidity and mortality in 1 to 2 years of postoperative [22]. When this occurrence is combined with low brain activity (low BIS), the risk of mortality can increase [23]. This questionnaire suggests that Portuguese anesthesiologists are aware of overshooting risks, however, not applied to prevent measures to avoid it, because there is no developed objective method that permits the precise identification of the moment of loss of consciousness yet.

The introduction of TCI systems has enabled relatively accurate dosing by continuous infusion, based on the pharmacokinetic models to titrate propofol administration to achieve specific plasma or effect-site drug concentrations in an average patient [24]. Various plasma administration and effect-site targeting TCI systems are commercially available to administer hypnotics and opioids. Currently, TCI systems are approved and available in more than 90 countries [25]. More than 60 000 units have been sold and are being used to provide TCI propofol-based intravenous sedation and anesthesia for millions of patients around the world every year [25]. Although TCI is a part of established practice around the world, TCI devices have not yet received regulatory approval in the United States [25]. Results showed that 36% of the Portuguese anesthesiologists never used TCI. This may be to the lack of knowledge on how to use these systems. The fact that most anesthesiologists that used the TCI system had chosen the TCI view mode (the learning mode of the TCI that uses a constant infusion only with a theoretical reference) maybe because they are not actually using the system to its purpose, which is to set a determined concentration of propofol and to maintain it during maintenance. In this manner, because anesthesiology is a pioneering specialty in the development and use of simulation tools, with positive results that impact clinical practice, an educational intervention should be adopted aiming at preparing not only students or residents of anesthesia but also specialized physicians. For example, to benefit from the usefulness of TCI systems, workshops could be

provided by the brands, training sessions at anesthesiology service meetings could be given, specialized physicians could be updated by other experts with more experience, and, maybe anesthesiology services could be sensitized to the importance of these systems and contribute for the acquisition of such tools.

As the main conclusion of this study, there appears to be a diversity in the amount and how propofol is used by the Portuguese anesthesiologists to induce general anesthesia. Results showed that there are a wide variety of methods for evaluating the loss of consciousness, a diversity in handling propofol in induction, a lack of experience in using target-controlled infusion systems, and in assessing the relationship between dose, velocity, and concentration of propofol. There were also some recommendations in this study for anesthesiologists to consider implementing them in their clinical practices. The intention is to forward the questionnaire to 40 international experts in the future to compare the results with other countries' results.

2.2 Overview of the current methods to monitor the depth of anesthesia and detect loss of consciousness

Ana Leitão Ferreira MSc, Catarina Nunes PhD, Joaquim Gabriel Mendes PhD, Pedro Amorim MD

Abstract

This review aims to give an overview of the current state of monitoring depth of anesthesia and detecting the moment of loss of consciousness, from the first clinical signs involved in anesthesia to the latest technologies used in this area. Such techniques are extremely important for the development of automatic systems for anesthesia control, including preventing intraoperative awareness episodes and overdoses.

A search in the databases Pubmed and IEEE Xplore was performed using terms such as anesthetic monitoring, depth of anesthesia, loss of consciousness, as well as anesthesia indexes, namely BIS.

Despite the several methods capable of monitoring the hypnotic state of anesthesia, there is still no methodology to accurately detect the moment of loss of consciousness during the induction of general anesthesia.

Keywords: depth of anesthesia, general anesthesia, loss of consciousness, patient monitoring.

Introduction

General anesthesia is a drug-induced, reversible condition that produces unconsciousness, analgesia, amnesia, and akinesia with the maintenance of physiological stability [26]. Of the behavioral state, unconsciousness is perhaps the most fascinating. Unconsciousness can be achieved by altering the patient's level of arousal and/or cognition by given them anesthetic drugs.

Induction of anesthetic drugs may be performed intravenously either using a constant-rate or an intermittent infusion (bolus), or instead, using a Target Controlled Infusion (TCI) system. TCI systems administer drugs based on the simulated concentration for a specific patient, usually considering the age, weight, height, and gender. These systems continuously simulate the drug concentration inside the human body and thus control the drug administration either by effect-site or by plasma concentration target steering. This means that the anesthesiologist may choose the drug target concentration for that specific patient based on the simulated expected response and administer the necessary dose to achieve the desired target automatically. TCI systems have been implemented in some commercially available electronic syringe pumps and may be used in the clinical environment.

There are various PK models for the use of drugs in TCI, while manual infusion can be carried out with or without an initial bolus, though with no bolus it takes a long time to achieve the desired hypnotic effect. For the use of propofol in TCI, the most well-known PK models are Marsh's [27] and Schnider's [28]. For remifentanil, fentanyl/alfentanil and fentanyl the most used PK models are Minto's [29], Shafer's [30], and Hudson's [31], respectively. Although TCI systems are commercialized in several countries, the United States of America Food and Drug Administration (FDA) has not yet approved it.

Loss of consciousness (LOC) occurs during the induction of general anesthesia. Detecting the moment the patient loses consciousness has an important role in the induction of general anesthesia. Identifying the precise moment of LOC will allow determining the individual response of each patient to the hypnotic and will provide important information to guide the infusion rate required to maintain an adequate level of anesthesia, ensuring safe and effective care. This will help to prevent intraoperative awareness episodes and overdose, two serious and frequently preventable problems that have gained attention from clinicians and patients alike.

Intraoperative awareness occurs when a patient under general anesthesia regains consciousness with recall during intraoperative events. It is usually the result of insufficient hypnotics and is considered a very traumatic experience that causes long term morbidity in some patients [27][28]. The incidence rate of awareness established by large multicenter studies was approximately 1-2 per 1000 cases. Moreover, awareness during anesthesia is a reason for compensation claims [32], even if they may depend on social or cultural factors. No recent studies are analyzing this phenomenon, and the medical and legal consequences of intraoperative awareness have yet to be clarified.

Overdose is a stage reached if the patient received too much hypnotic drug and it may be a consequence of an overshooting of the control system, which is a phenomenon that occurs due to another relevant characteristic known as hysteresis [11]. For a better understanding of this phenomenon, Figure 2.1 (A and B) presents an example of a simulation made for an infusion rate of propofol of 1200 mL/h and 200

mL/h until LOC, respectively. Hysteresis is the time delay between the peak of plasmatic concentration (Cp) and the peak of the effect-site concentration (Ce). This leads to an increasing in Ce, even after the infusion is stopped. The difference between the maximum value of Ce and the effective Ce at LOC is then described as overshoot. The magnitude of the overshoot and hysteresis depends on the pharmacokinetic model. Overdose may lead to the severe brain stem or medullary depression, which can result in respiratory and cardiovascular collapse, which can be fatal. From a pharmacological point of view, excessive hypnotic drug dosages will increase the probability of a delayed recovery due to the accumulation of anesthetic drugs in the fatty tissues of the patient [33]. The importance of administering hypnotic slowly to avoid an overdose is widely accepted [16]. Studies have shown that the required doses for anesthesia onset were affected by changes in the rate of injection [16][34]. The use of a slow infusion rate results in a longer induction duration, but requires a lower total dose, and results in a lower incidence of apnea and decrease of blood pressure [19].

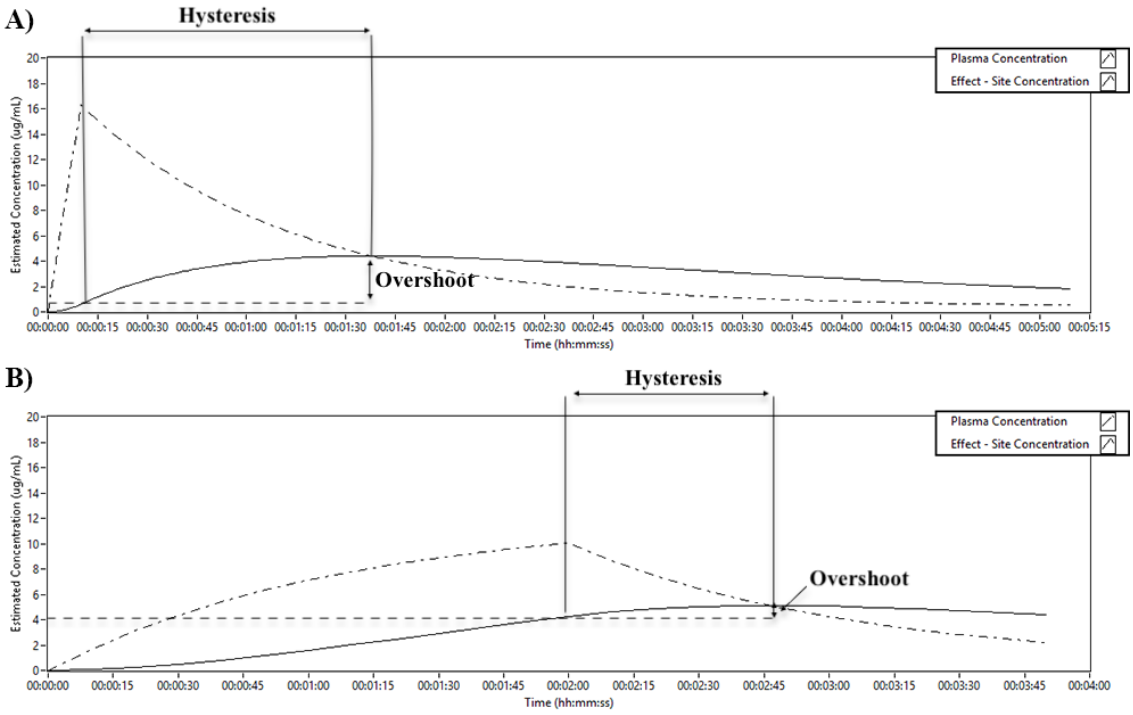


Figure 2.1 Overshoot and hysteresis between plasmatic and effect-site concentration of propofol (mg/mL) versus time for different infusion rates of propofol: A) 1200 mL/h until LOC (14 seconds); B) 200 mL/h until LOC (2 minutes).

Thus, controlling the level of anesthesia is very important during routine anesthesia. However, due to the fuzziness of depth of anesthesia, controlling the anesthesia is still a hard-to-reach goal. In the absence of an incontrovertible definition of depth of anesthesia, a variety of methods for the assessment of the hypnotic component of anesthesia exists. An excellent and exhaustive, non-systematic review that proposes the usefulness of hypnotic depth monitoring is presented in the work of Rodríguez at al [35]. There are both, subjective and/or objective methods. Subjective methods rely on the movement and autonomic response to some stimuli and depend on the opinion and experience of the anesthesiologist. The objective

methods rely on the sensitivity and accuracy of a monitor. A detailed description of subjective and objectives methods to assess the hypnotic component of anesthesia is presented hereafter, in the state-of-the-art section of this manuscript. Despite the existence of a variety of methods to assess the hypnotic component of anesthesia, there are no reliable ways to be certain when the patient has transited from the conscious to the unconscious state. Identifying the precise moment of LOC during the induction phase of general anesthesia is extremely important because it will determine the hypnotic amount required for each patient and will provide important information to guide the infusion rate required to maintain an adequate level of anesthesia, ensuring a safe and an effective care.

This review aims to give an overview of what is the current state of knowledge on anesthetic monitoring systems and the detection of drug-induced loss of consciousness, from the first clinical signs involved in anesthesia to the latest technologies used in this area.

Methods to assess the hypnotic component of anesthesia

a) Subjective Methods

During induction of anesthesia, to determine if a patient is conscious or unconscious, a dichotomous "all-or-none" assessment of responsiveness can be performed in clinical practice. This dichotomous assessment is possible using the isolated forearm technique (IFT): a tourniquet is placed on the patient's forearm with the cannula proximal to this tourniquet or on the other arm. During anesthesia, the patient is asked to squeeze a hand, indicating that the patient may be awake and able to interact until he (or she) does not respond anymore. Despite being a simple technique and an interesting research tool, the isolated forearm has limitations as a monitor of the depth of anesthesia: very low sensitivity and specificity; the levels of anesthesia desired to prevent movements in patients are more meaningfully, higher than those usually used, since the advent of muscle relaxant; patients have stated that they heard commands to move the isolated arm, but were unable to do so, even though nerve simulator suggested that the arm was not paralyzed and non-specific startle responses interpreted as consciousness.

Loss of response to name-calling, to verbal command, or a painful stimulus and loss of eyelash reflex are also used: the anesthetist repeats the stimulus at a constant interval until the patient does not respond anymore.

To standardize the clinical signs of hypnotic drug onset and offset, the Modified Observer's Assessment of Alertness and Sedation Scale (OAA/S) [36], derived from the original Observer's Assessment of Alertness/Sedation scale [36], originally validated for use with midazolam, was introduced. The OAAS describes the level of sedation on a numerical scale, ranged from 0 to 5, where the observer rates patient responsiveness, speech, and facial expression/eye movements. The modified form uses only the responsiveness component of the original scale [Unresponsive (1) -Awake (5)].

These clinical observations are used in daily practice due to their simplicity. However, they are very imprecise and depend on the patient's collaboration. Clinical signs are based on a voluntary act by the patient and often fail because patients lose critical judgment before losing consciousness. Besides that, as

the dose of hypnotic is increased during induction, the patient may enter a state of paradoxical excitation because the drug is intended to induce unconsciousness, but the stimulus induces excitation instead.

b) Objective Methods

Due to the limitations of the clinical observations of anesthetic drug effect, continuous monitors of the hypnotic component of anesthesia were developed. The transition from consciousness to unconsciousness occurs in the brain; therefore, the level of anesthesia is measured on the main target organ of anesthesia, the brain. Monitoring the electrical activity of the brain to assess the anesthetic effects uses Electroencephalography (EEG) activity from electrodes placed on the forehead of the patient. Two types of electrical signals can be further divided into those that process spontaneous EEG and Electromyography (EMG) activity or those based on Evoked Potentials (EP).

EEG measures the spontaneous electrical activity of the brain which may be measured using non-invasive electrodes attached to several locations of the patient's head (it is available an international system to aid consistent electrode placement [37]). In general, anesthetics produce a frequency shift of the EEG signal, from high to low frequencies and an increase of the EEG signal amplitude, creating an EEG signal with synchronous properties. Typically, the EEG spectrum is divided into five frequency bands called delta (0.5-4 Hz), theta (4-8 Hz), alpha (8-13 Hz), beta (13-30 Hz), and gamma (> 30 Hz). Each band has a different behavior under the effect of hypnotics, and it depends on the type of administered anesthetic drug. Propofol, the most used hypnotic drug for general anesthesia, changes the EEG from a low-voltage, high-frequency awake signal to a progressive high-amplitude, low-frequency signal.

EPs are detected by electrodes that are positioned over the primary receiving area for a visual, auditory, or somatosensory stimulus. The patient is subjected to a large number of repeated stimuli and the EEG is recorded during a fixed period after each one. The signal is then amplified before the EPs are extracted by taking the average of the responses. All EP responses are described in terms of latency (the time from the stimulus until the response) and amplitude (the size of the response). Auditory Evoked Potentials (AEP) are the most used EPs to evaluate general anesthesia. A functional auditory system is a basic requirement for AEP analysis. According to latencies, the AEP is divided into three components: early component (latencies < 10 ms), middle component (latencies 10 – 50 ms) and late component (latencies > 50 ms). The early component is relatively resistant to the effects of anesthesia while the late component disappears with low concentrations of anesthetic. During anesthesia, the middle component increases on latency and decreases on amplitude.

Studies have provided moderate-quality evidence that optimized anesthesia guided by EEG or EPs indices probably reduces the risk of postoperative delirium in patients aged 60 years or over undergoing non-cardiac surgical and non-neurosurgical procedures[38] and reduces the risk of patient awareness during surgical procedures [39].

There are much different EEG-based depth of anesthesia monitors which leads to anesthesia indexes, including the Bispectral Index System Monitor (BIS Monitor; Covidien, USA); Entropy Module (GE

Healthcare, USA); Narcotrend (MonitorTechnik, Germany); Patient State Index Monitor, SEDLine (Masimo, USA); Cerebral State Monitor (Danmeter, Denmark); loC-View Monitor (Aircraft Medical, Barcelona, Spain); qCon (Quantium Medical, Spain) and AEP Monitor (Danmeter, Denmark). In general, the commercial monitors of the depth of anesthesia use a dimensionless monotonic index as a measure of the depth of anesthesia, typically scaled from 100 (awake state) to 0 (deep coma).

Bispectral Index (BIS)

The Bispectral Index (BIS) combines the Fast Fourier Transformation (FFT) with a quadratic analyzing model for the EEG, the bispectral analysis. Therefore, the BIS consists of the following four subcomponents: the bispectral component SyncFastSlow (log (bispectrum (0.5Hz-47 Hz)/bispectrum (40-47 Hz)), the spectral component BetaRatio (log (power (30–47 Hz)/power (11–20 Hz)), the burst suppression ratio (BSR) and the QUAZI suppression component. The resulting bispectral index, BIS, is a nonlinear combination of these four sub-parameters.

Entropy Module

The entropy is by definition a measure of disorder, irregularity, complexity, and prediction of a signal. During general anesthesia, the Entropy module relies on a method of assessing the degree of irregularity in EEG signals, which changes from irregular to more regular patterns when anesthesia deepens. The entropy module calculates two parameters: Response Entropy (RE), Shannon entropy of the power spectrum (0.8–47 Hz) and State Entropy (SE) Shannon entropy of the power spectrum (0.8–32 Hz).

Narcotrend

The Narcotrend monitor automatically analyses the raw EEG using spectral analysis to produce six states of hypnosis, which are then translated into 15 different patterns evidenced during anesthesia. Each of these stages was used to calculate Narcotrend Index from a set of EEG parameters, including spectrum, entropy and autoregression.

Patient State Index (PSI), SEDLine

The SedLine monitor measures the effects of anesthesia and sedation by monitoring both sides of the brain's electrical activity to enable more individualized titration and improve the care of patients under anesthesia or sedation. The result is a Patient State Index (PSI) value, which is calculated by an algorithm that combines several parameters of frequency analysis: absolute power gradient between frontopolar and vertex regions in the gamma band; absolute power changes between midline and central regions in beta and between midline frontal and parietal regions in alpha frequency; total spectral power (0.5–50 Hz) in the frontopolar region; mean frequency of the total spectrum in midline frontal region; absolute power in delta frequency at the vertex and posterior relative power in the slow delta range. All parameters are included in a plausibility analysis to calculate the PSI. Additionally, surrogate analysis is performed by calculating burst suppression and arousal detection, which means that these parameters modulate the PSI index in the

case when the signal quality is under question. Finally, before the index is displayed, it is post-processed with an averaging algorithm, to provide a more stable output.

Cerebral State Monitor

The Cerebral State Monitor combines four sub-parameters extracted from the EEG to calculate a Cerebral State Index (CSI). These parameters are: the spectral parameters beta ratio (log E(30 – 42.5 Hz)/E(11-21 Hz), alpha ratio (log E(30 – 42.5 Hz)/E(6 -12 Hz)), beta-alpha ratio (log E(6-12 Hz)/E(11 -21 Hz)), and the burst suppression ratio. Afterward, all parameters are fed to a fuzzy logic interference system to calculate the CSI index.

loC-View Monitor (IoC)

The loC-View Monitor displays the Index of Consciousness (IoC). It uses three sub-parameters to calculate the IoC: symbolic dynamics that detect the complex non-linear properties of the EEG; beta ratio (during superficial anesthesia) and the amount of burst suppression of the EEG (during deep anesthesia). All these parameters are then combined through a set of fuzzy logic rules into a single index.

qCon

The anesthetic depth monitor *qCon* was developed for determining the probability of response to pain and nociception of a subject during different levels of arousal. It defines an index of consciousness (qCon) from the EEG raw data, calculated based on Adaptive Fuzzy Interference Systems (ANFIS).

AEP Monitor

AEP monitor uses autoregressive models with exogenous input (ARX) to detect the AEP and then calculate the AEP – ARX – Index [or A-line Autoregression Index (AAI) autoregressive index]. The AEP is detected in the frequency range 25–65 Hz, using ARX. After the ARX analysis, the reconstructed amplitudes and latencies are evaluated and, in the meanwhile, an undisclosed algorithm is used to analyze the EEG in the frequency band between 3-47 Hz. The decision of how the AAI is constructed from AEP and EEG analyses is made by the weighting function, based on the signal-to-noise ratio. The AEP-Index (AEPex) is exclusively based on an AEP parameter that is the morphology of the AEP signal.

Table 2.3 are presented the recommended ranges for the referred indices of the hypnotic component of anesthesia. As it can be observed, these ranges differ from index to index. BIS, entropy, CSI, and IoC indicate that adequate anesthesia will occur for values between 40 and 60, the other indices consider different ranges. Although multiple indices have been developed, some incorporated in commercialized devices and others only developed for academic purposes, only BIS and Entropy have had a significant commercial impact. On the one hand, spontaneous EEG monitoring has several confounding factors that may impede the interpretation of EEG-derived indices and may lead to erroneous conclusions. They include artifacts from the surrounding environment, interindividual variability in terms of baseline EEG characteristics, erroneous site of EEG recording, the delay between EEG acquisition, and value display,

specific clinical conditions and the effect of the interactions between different anesthetics. On the other hand, the use of AEPs is not very reproducible as there are large interindividual differences of response to different anesthetic regimens. Additionally, although anesthesiologists provide care of thousands of patients daily, only about half use depth of anesthesia monitors.

Methods

Studies containing trials with subjects submitted to intravenous drug administration for anesthesia, whose authors pointed out the values of the monitoring indexes at the time of LOC were considered. Studies were identified by searching electronic databases for reference articles. No limits were applied for language, thus foreign papers were translated. This search was applied to PubMed (2004-Present) and IEEE Xplore Digital Library (2004-Present). The last search was run on 30 April 2018.

The search was performed using the following terms (in all clinical trials and databases): death anesthesia, monitoring, loss of consciousness, clinical trials, humans, BIS and each of the existing indexes. The following information was extracted from each trial: (1) trial's inclusion and exclusion criteria; (2) anesthetic protocol for induction, inclusion of pre-medication, type of drugs, dose and pharmacokinetic models; (4) method to assess the moment of LOC, including the used index; and last, (5) values of the different indexes at LOC.

In all studies the primary outcome assessed was the value of the hypnotic index at the moment of LOC. Secondary outcomes were the anesthetic protocol and the type of clinical judgment of LOC.

Quantitative analyses were performed in order to compare the values of the different indexes at LOC within the several anesthetic protocols and clinical assessment of LOC.

Results

A total of 35 studies were identified for inclusion in this review. The search on databases provided a total of 304 citations. After removing duplicates, remained 145 articles. Of these, 82 were discarded because after reviewing the abstracts it appeared that these papers clearly did not meet the criteria. 5 additional studies were discarded because the full text of the study was not available, or the paper could not be accurately translated into English. The full text of the remaining 77 citations was examined in more detail. A total of 42 studies were excluded because they did not meet the inclusion criteria. The main exclusion criteria entailed no drugs affecting the different techniques of monitoring depth of anesthesia: patients had not been given pre-medication prior induction of anesthesia or other sedatives intake.

Table 2.3 Recommended ranges for the different EEG-based indices of the hypnotic component of anesthesia. Values are unitless and range from 0 to 100.

Depth of anesthesia indexes / Hypnotic component of anesthesia	BIS	Entropy	Narcotrend	PSI	CSI	IoC	qCon	AAI	AEPex
EEG suppression	-	-	-	0 - 5	0 - 10	0 - 40	-	-	-
Burst suppression	0 - 20	-	0 - 15	-	-	-	-	-	-
Deep anesthesia	20 - 40		15 - 35	5 - 35		0 - 40	20	0 - 15	0 - 25
Deep anesthesia with burst suppression	-	0 - 40	-	-	10 - 40	-	-	-	-
Anesthesia	40 - 60	40 - 60	35 - 65	30 - 65	40 - 60	40 - 60	40 – 60	15 - 25	25 - 45
Sedation	60 - 80	-	65 - 95	65 - 85	60 – 90	60 - 80	75	25 - 40	45 - 60
Awake	80 -100	60 - 90	95 - 100	85-100	90-100	80-100	80-100	40-100	60-100

Thirty-five studies met the anesthetic protocol criteria and were included in the systematic review. No unpublished relevant studies were obtained.

Summary of included studies reporting the values of each index at the moment of LOC are presented in Table 2.4

From the 35 articles analyzed, 12, 8, 2, 4, 2, 1, 4, and 2 studies identifying respectively BIS, Entropy, PSI, CSI, Narcotrend, IoC, qCon, and AAI values at LOC. The average values at LOC for BIS vary between 42 and 75.4, for entropy vary between 34 and 79, for PSI 30 – 45, for CSI between 56 and 72.6, Narcotrend 44.3 – 58.3, qCon 21.33 – 67.72 and AAI 30 – 57. In most cases, the deviation from the average value is very significate, which means that there is a larger interindividual variability. It is also important to note that there is a strong dependence of these values with the applied anesthetic protocol: at LOC it could be present only hypnotic, both hypnotic and analgesic, or only analgesic.

According to the clinical criteria used to determine the moment of LOC, different index values are also obtained: these criteria are therefore not coincident in time, so a systematic error may occur by associating all the index values to the same moment of LOC. Even when the same clinical criteria and the same anesthetic protocol are used, one can also observe a large variation in the values associated with LOC. No study that analyzed the entropy index used the OAAS scale to determine the moment of LOC. Only one study was found in the literature using the IoC at LOC. Some indices have extremely high sensitivity and specificity in identifying consciousness and unconsciousness but none of them can detect the transition between both states or detect the moment of LOC precisely.

Discussion

Closed-loop systems have been developed to control the administration of drugs during anesthesia and using BIS as a target for control. Studies have been made to investigate the performance of the seven different closed-loop systems: CLADS [40], Rugloop [41], HSS [42], Infusion Toolbox 95 [43], Self-Designed Interface [44], McSleepy [45], CONCERT-CL [46] and Monitor [47]. When compared with manual control, these BIS-guided systems reduce propofol requirements during induction, better maintain a target depth of anesthesia, and reduce recovery time [48]. Given the interindividual variability observed from the studies presented in Table 2 for the index values at LOC, the adequacy of these closed-loop systems is questionable since all of them assume that the same amount of drug is administrated to any patient in any anesthetic protocol.

From the studies presented in Table 2.4, it is important to refer that the indices have three major drawbacks: the recordings from the monitors include artifacts that arise from movements, electrical interference, noise from electrodes, and quantification error in the analog to digital conversion; they require some time to process the algorithms to compute the indices that may take several seconds or even minutes, which, for induction administration can results in excessive anesthesia with clinical consequences; and, although the raw EEG and its frequency components can give direct, detailed information about brain states under anesthesia, most current brain monitoring systems reduced the complex EEG signal to a single number that could not accurately reflect the underlying physiological processes that create the patterns.

Propofol is one of the most commonly used anesthetic drugs. A very relevant study from Purdon et. al [49] took highly detailed EEG readings of 10 healthy volunteers during propofol general anesthesia, whose dosage was slowly increased to a target level then slowly decreased, while study participants listened to pre-recorded sounds presented every four seconds and were asked to identify the type of sound they heard by pressing a button. A loss of response to clicks indicated the onset of sedation, and a persistent loss of response to words was considered loss of consciousness. The readings identified characteristic changes in EEG patterns that indicated sedation, loss, and return of consciousness, and a state of profound unconsciousness. One particular pattern, which the researchers called "trough-max" occurred during transitions in consciousness. The consequences are huge because it would mean they have found a brain state where they know patients will be unconscious and could monitor the brain state in the operating room using EEG. With these fundamental neurophysiological markers of the sedative and unconscious states under propofol and with some existing EEG equipment, it may be possible to start monitoring EEG signatures when administering propofol. This may be seen as an introduction to new control systems endpoints.

Conclusion

Concluding, clinical signs allow anesthesiologists to decide whether a patient is (or is not) unconscious during induction of hypnotics under general anesthesia, but they do not provide information on the precise time when the transition from consciousness to unconsciousness occurs. That is because either the patients do not lose all reflexes simultaneously, or the verification of such signs is in most cases evaluated discontinuously.

With anesthesia monitors based on EEG and AEP, continuous monitoring response signals allow anesthesiologists to directly evaluate the patient's brain activity over time. However, studies showed how these monitors fail in identifying the instant at which consciousness is lost. The computation delays, the difficulty in separate the different electrical signals produced by the body, and the large interindividual variability of the monitor indices make them good indicators of the evolution of the patient during the procedure, but not good to indicate the moment of loss of consciousness.

Other studies showed that combining the use of depth of anesthesia monitors with the information provided by the clinical signs reduced the incidence of intraoperative awakening and overdosing. However, it continues to be justified to develop a system that detects the exact moment in which the patient loses consciousness. Identifying this moment during the induction phase of general anesthesia will determine the hypnotic amount required for each patient and will provide important information to guide the infusion rate required to maintain an adequate level of anesthesia, ensuring safe and effective care. This could open the door to automated systems based solely on the patient state of consciousness, in addition to substantially contribute to significant advances in the field of anesthesia itself. Furthermore, detecting the moment patients lose consciousness is the first step to develop a fully automated anesthesia personalized delivery systems based on the conscious state of the patients.

Table 2.4 Indicative values of the loss of consciousness moment. The values for the loss of consciousness are expressed in "Mean (Standard Deviation)", "Mean (Maximum-minimum)", "Mean" according to the corresponding authors. The acronyms mean: BIS – Bispectral Index; SE – State Entropy; RE – Response Entropy; PSI – Patient State Index; CSI – Cerebral State Index; IoC – Index of Consciousness; AAI - AEP Index.

Source	Depth of anesthesia index	Values at loss of consciousness	Anesthetic technique	Clinical judgment of loss of consciousness
[50]	BIS	58 (58-59)	Propofol (TCI: Marsh's model) + Remifentanil (TCI: Minto's model)	OAAS less than 1
[51]		63.2 (60.3-66.9) 71.1 (67.6-74.5) 71.4 (68.9-73.7)	Propofol (TCI: Marsh's model) Dexmedetomidine (0.5µg/kg) + Propofol (TCI: Marsh's model) Dexmedetomidine (1.0 µg/kg) + Propofol (TCI: Marsh's model)	OAAS less than 2
[52]		42	Propofol (TCI: Schnider's model)	Verbal command or eyelash reflex
[53]		58 (40-70)	Propofol (TCI: Schnider's model)	OAAS less than 2
[54]		50 (17)	Etomidate 0.2% (300 mg/kg)	Eyelash reflex
[55]		65 (18)	Remifentanil (TCI: Minto's model) + Propofol (600mL/h)	OAAS less than 2
[56]		61.5 (18.7) 73.8 (15.1)	Ropivacaine 0.2% + Propofol (TCI: Marsh's model) Ropivacaine 1% + Propofol (TCI: Marsh's model)	Verbal commands, dropping a syringe or eyelash reflex
[57]		60 (15) 75 (18)	Propofol (TCI: Marsh's model) Propofol (TCI: Marsh's model) + NO_2 67%	Eyelash reflex
[58]		69.5 (15.8)	Remifentanil (TCI: Minto's model) + Propofol (Schnider's model)	Verbal commands and tap on the forehand

Source	Depth of anesthesia index	Values at loss of consciousness	Anesthetic technique	Clinical judgment of loss of consciousness
[59]		74.1 60.8	Propofol (30 mg/kg/h) + Fentanyl (2 µg/kg) Propofol (30 mg/kg/h)	Verbal commands
[60]		60.5 (58-63) 69.5 (67.8-71.1) 74.6 (72.9-76.2) 66.2 (62.6-69.1) 74.6 (72.9-76.2)	Placebo + Propofol (Marsh's model) Fentanyl (TCI: Shafer's model) + Propofol (Marsh's model) Alfentanil (TCI: Shafer's model) + Propofol (Marsh's model) Sufentanil (TCI: Hudson's model) + Propofol (Marsh's model) Remifentanil (TCI: Minto's model) + Propofol (Marsh's model)	OAAS less than 3
[61]		46.6 (42.9-50.4) 61.3 (57.3-65.3) 75.4 (70.4-80.4)	Propofol (300 mL/h)	Eyelash reflex Verbal contact Drop syringe
[52]	**SE**	37	Propofol (TCI: Schnider's model)	Verbal command or eyelash reflex
[62]		75 (11)	Remifentanil (TCI: Minto's model) + Propofol (TCI: Schnider's model)	Verbal commands and gentle shaking
[63]		67 (5-89)	Propofol (1mg/kg/min)	Dropping a bottle
[64]		34 (17-70)	Propofol (15 mg/min)	Verbal commands
[52]	**RE**	44	Propofol (TCI: Schnider's model)	Verbal commands, eyelash reflex
[62]		79 (14)	Remifentanil (TCI: Minto's model) + Propofol (TCI: Schnider's model)	Verbal commands and gentle shaking
[63]		79 (20-99)	Propofol (1mg/kg/min)	Dropping a bottle

Source	Depth of anesthesia index	Values at loss of consciousness	Anesthetic technique	Clinical judgment of loss of consciousness
[64]		40 (23-76)	Propofol (15 mg/min)	Verbal commands
[65]	**PSI**	32 (7)	Propofol (2.3±1.9mg/min) + Sufentanil (5.6±4.5µg/min)	Ramsay sedation score = 6
[66]		45 39 30 42	Propofol (TCI: Schnider's model) Sevoflurane (0.5-4.5 vol%) Propofol (TCI: Schnider's model) + Remifentanil (TCI: Minto's model) Sevoflurane (0.5-4.5 vol%) + Remifentanil (TCI: Minto's model)	MOAAS = 2
[67]	**CSI**	71.2 (18.1) 58.5 (11.6)	Sevoflurane (5 vol%) + Remifentanil (0.2µg/kg) Propofol (0.7 mg/kg) + Remifentanil (0.2µg/kg)	Verbal commands
[68]		70 (4) 71 (2)	Propofol (1.8 mg/kg) Propofol (TCI: Schnider's or Marsh's model)	Verbal commands
[69]		56 (40-76)	Propofol (15 mg/min)	Verbal commands
[61]		58.7 (55.1-62.2) 64.2 (60.6-67.8) 72.6 (68.7-76.5)	Propofol (300 mL/h)	Eyelash reflex Verbal commands Drop syringe
[70]	**Narcotrend**	58.3 (17.5)	Remifentanil (1 µg/kg) + Propofol (2 mg/kg)	Verbal commands

Source	Depth of anesthesia index	Values at loss of consciousness	Anesthetic technique	Clinical judgment of loss of consciousness
[71]		47 (7.2) 44.3 (8.7)	Propofol (TCI: Marsh's model) Sevoflurane 8%	Eyelash reflex
[72]	**IoC**	47.3 (3.7)	Sevoflurane 8%	OAAS less than 1
[73]	**qCon**	67.72 (17.88) 58.27 (16.80)	Propofol (TCI: Schnider's model) + Remifentanil (TCI: Minto's model)	Verbal commands Eyelash reflex
[74]		55 (16)	Propofol (TCI: Schnider's model) + Remifentanil (TCI: Minto's model)	Eyelash reflex
[72]		21.33 (6.11)	Sevoflurane 8%	OAAS less than 1
[59]		32.9 31.8	Propofol (30 mg/kg/h) + Fentanyl (2 µg/kg) Propofol (30 mg/kg/h)	Verbal commands
[75]	**AAI**	57 (13)	No pre-medication Propofol (2 mg/kg) + Fentanyl (1 µg/kg)	Verbal commands, eyelash reflex
[76]		30 (20-39)	Propofol (TCI: Schnider's model)	Eyelash reflex

3 PROPOFOL REQUIREMENTS AT LOSS OF CONSCIOUSNESS

This chapter is divided into two main sections, section 3.1 presents the studies developed to quantify the inter-patient variability of the concentration of propofol required for the loss and recovery of consciousness and the identification of predictive factors. Section 3.2 presents an observational study to evaluate the time delay on BIS index in response to anesthesia induction. Section 3.3 presents a developed model to predict the amount of propofol patients need to lose consciousness.

The studies described in the first section led to four abstracts published in the Journal of Neurosurgical Anesthesiology: two from the 43rd SNACC Annual Meeting 2015, one from the 44th SNACC Annual Meeting 2016 and one from the 45th SNACC Annual Meeting 2017:

i. High variability in propofol requirements for anesthesia induction is shown independently of remifentanil; Journal of Neurosurgical Anesthesiology 2015, Volume 27, Number 4.
ii. Inter-patient variability and predictive factors of propofol requirements and estimated concentration for loss of consciousness and recovery; Journal of Neurosurgical Anesthesiology 2015, Volume 27, Number 4.
iii. Wide inter-patient variability in metabolism measured by indirect calorimetry during general anesthesia and surgery does not influence propofol requirements; Journal of Neurosurgical Anesthesiology 2016, Volume 28, Number 4.
iv. Towards personalized anesthesia: predictive factors for propofol requirements for loss of consciousness; Journal of Neurosurgical Anesthesiology 2017, Volume 29, Number 4.

The study presented in the second section led to a published paper:

i. Evaluation of Bispectral Index time delay in response to anesthesia induction: an observational study; Brazilian Journal of Anesthesiology 2019; 69(4):377-382.

The study presented in the third section led to a published paper:

i. Neuro-fuzzy models to predict the required propofol amount for loss of consciousness during general anesthesia: a preliminary study; Proceedings of the IEEE International Symposium on Medical Measurements and Applications (MEMEA), 2018; 587-591.

This chapter is organized as follows:

3.1 Quantification of the inter-patient variability of the amount of propofol required for the loss of consciousness and identification of predictive factors.

3.2 Evaluation of Bispectral Index time delay in response to anesthesia induction: an observational study.

3.3 Neuro-fuzzy models to predict the required propofol amount for loss of consciousness during general anesthesia: a preliminary study.

3.1 Quantification of the inter-patient variability of the amount of propofol required for the loss of consciousness and identification of predictive factors

Ana Leitão Ferreira MSc, Ana Catarina Dias MD, Catarina Nunes PhD, Joaquim Gabriel Mendes PhD, Pedro Amorim MD

Abstract

Objectives: The present study aims at assessing inter-patient variability in propofol requirements for loss and recovery of consciousness and identifying predictive factors related to it.

Methods: Variability was assessed on inductions with, in this order, propofol, and remifentanil, remifentanil and propofol, and fentanyl and propofol. Rugloop software collected the data. Statistics were Pearson or Spearman correlations, linear regression, Shapiro-Wilk test, and 2 Way-ANOVA. Results were mean±standard deviation.

Results and conclusion: When anesthesia induction started with propofol followed by remifentanil, propofol effect-site concentration at the loss of consciousness was 5.14±1.01 ug/mL with 271% variability. When anesthesia induction started with remifentanil followed by propofol, propofol effect-site concentration at the loss of consciousness was 4.07±1.17 ug/mL with 453% variability. When anesthesia induction started with fentanyl followed by propofol, propofol effect-site concentration at the loss of consciousness was 4.23±1.58 ug/mL with 539% variability. The present study shows a wide inter-patient variability for propofol requirements at the loss of consciousness, which is clinically relevant. These results already considering the variables age, gender, weight, and height, meaning that the pharmacokinetic and pharmacodynamic models may not incorporate these variables appropriately. Induction with propofol should be performed anticipating a variability of more than 200% between patients.

Introduction

General anesthesia includes four main components: unconsciousness (hypnosis and amnesia), antinociception, immobility, and hemodynamic stability [26]. It can be described concerning the three periods: induction, maintenance, and emergence. General anesthesia is the most frequently used anesthetic technique to perform complex surgical interventions and is mainly characterized by the loss of consciousness of a patient. Here, attention is focused on the induction because is where the transition from unconsciousness occurs.

To render the patient unconscious, physician anesthesiologists use a combination of anesthetic drugs, including propofol. Propofol is the most commonly used intravenous agent for induction of anesthesia. Its advantages include its rapid onset, short duration of action, minimal side effects, and rapid recovery with reduced postoperative nausea and vomiting. Delivery of propofol can be performed manually or, as usually performed nowadays, with a computer-assisted Target Controlled Infusion (TCI) system. Along with the administration of propofol, short-acting opioid doses such as remifentanil or fentanyl can be used. The safety of the TCI systems in the administration of different intravenous agents, including propofol, remifentanil, and fentanyl has been documented [77]. TCI systems exploit pharmacokinetic (PK) and pharmacodynamic (PD) models of the drugs to predict and target drug concentrations and clinical effects. The most used and available TCI systems for propofol, remifentanil and fentanyl are the Schnider's [14][28] and Marsh's [27] PK model, the Minto's [78] and the Shafer's [30], respectively. However, most PK and PD models are developed for a general population rather than an individual subject. Therefore, the prediction accuracy of these population-based PK and PD models is limited by the inter-patient variability. In a previous study, Iwakiri and colleagues found the differences between the minimum and the maximum values for the concentrations of propofol at the loss of consciousness (LOC) very wide [79]. However, this large variability was not clearly quantified. In fact, the wide inter-patient variability in the propofol Ce concentration at LOC would make the quantification of the minimum concentration required for LOC difficult. This would not be important if large doses of propofol were well-tolerated. However, the respiratory depression caused by propofol induction is developed at the individual concentration at LOC. There are convincing clinical reasons to restrict the administration of propofol to the minimum effective concentration. In the absence of individual PD information, propofol continues to be usually administered according to the average population requirements. So, it is important to assess the magnitude of the individual variability of the propofol dose required for LOC.

Therefore, the present study aims at analyzing the inter-patient variability of the propofol Ce concentration required for LOC in patients subjected to induction of general anesthesia with Group 1 – propofol until LOC followed by remifentanil; Group 2 – remifentanil and propofol until LOC; and Group 3; fentanyl and propofol until LOC. The second aim of this study was to identify the predictive factor of the propofol Ce concentrations at LOC in all groups.

Materials and methods

Seventy-six patients have been retrospectively studied (Ref. 064-14 (042-DEFI/063-CES), Appendix B), using a pre-existing database, to analyze the inter-patient variability of the amount of propofol necessary for the loss of consciousness in patients whose induction started with propofol followed by remifentanil after LOC (Group 1). Also, 141 patients have been retrospectively studied, also using a pre-existing database, to analyze the inter-patient variability of the amount of propofol necessary for the loss of consciousness in patients whose induction started with remifentanil followed by propofol until LOC (Group 2). A total of 216 patients from these two groups were used to compare the induction response among them. Patients in Group 1 and 2, aged between 18 and 88 years old, were recruited for studies with institutional approval, and signed informed consent.

With the purpose of analyzing inter-patient variability of the amount of propofol necessary for the loss of consciousness in patients whose induction started with a bolus of fentanyl followed by a propofol infusion and identifying predictive factors of concentrations at the propofol effect-site (Ce) at LOC, 55 adult patients undergoing scheduled neurosurgeries have been recruited (Group 3). Inclusion criteria were patients between 18 and 80 years old, without serious cardiovascular, hepatic, or renal comorbidities and classified as ASA I to III on the scale of physical fitness assessment by the American Society of Anesthesiologists (ASA). All 55 patients signed informed consent and left with an explanation of what was going to be done and with the contact of the principal investigator in case of any doubt (see Appendix B_2).

All 216 patients from Group 1, 2, and 3 were weighed, the day before surgery, on a bioimpedance scale and assigned a random code of 12 algorisms to preserve their identity. After lying on the surgical table, all patients were covered with a sheet and a blanket folded in half inside, and at the level of the abdomen, a forced-air heating device was placed.

The following parameters were monitored in all patients: blood pressure (BP), pulse oximetry (SpO_2), heart rate (HR), electrocardiography (ECG), electromyography (EMG), Bispectral index (BIS), the temperature measured at the fingertip of the left hand, neuromuscular blockage in the right hand, esophageal temperature and cerebral oxygenation (Near InfraRed Spectroscopy - NIRS) with an INVOS monitor Figure 3.1). In some patients, the Analgesia Nociception Index (ANI) monitor has also been used. A vein was catheterized in the left hand where the serum was infused at a rate of 7 mL/kg/h. 100% O2 was administered through a facial mask. The continuous registration of these parameters was performed by Rugloop software on a dedicated computer (Figure 3.1). This software communicated with the Datex Ohmeda Aisys/GE monitor to obtain patient monitoring data and communicated with the TCI system (Fresenius Base Primea Orchestra) used for the administration of propofol and remifentanil.

Rugloop is a software that records all parameters every 5 seconds and exports them in its own format. The exported documents open with the LabGrab software, in which all the variables to be studied are chosen and exported as a format compatible with Excel software for later analysis.

The doses of fentanyl used in Group 3 were calculated and simulated with the Shafer model [30] in the Tiva TrainerX software for iPad.

Anesthetic protocol

Group 1

In the 75 patients of this group, intravenous infusion of 1% propofol started in TCI View mode (Schnider's model) [28] at 3.3mL/kg/h until LOC, identified as lack of eye-opening to name-calling and tap on the forehead. The Ce concentrations of propofol at LOC were noted and the Fresenius Base Primea system was switched to TCI mode, with a Ce concentration of propofol lower than the Ce at LOC, through the application of a previously presented formula [80]. Remifentanil infusion started with an effect-site concentration of 2.5ng/mL [78]. The moment of LOC and the 10 minutes after LOC were the two moments analyzed.

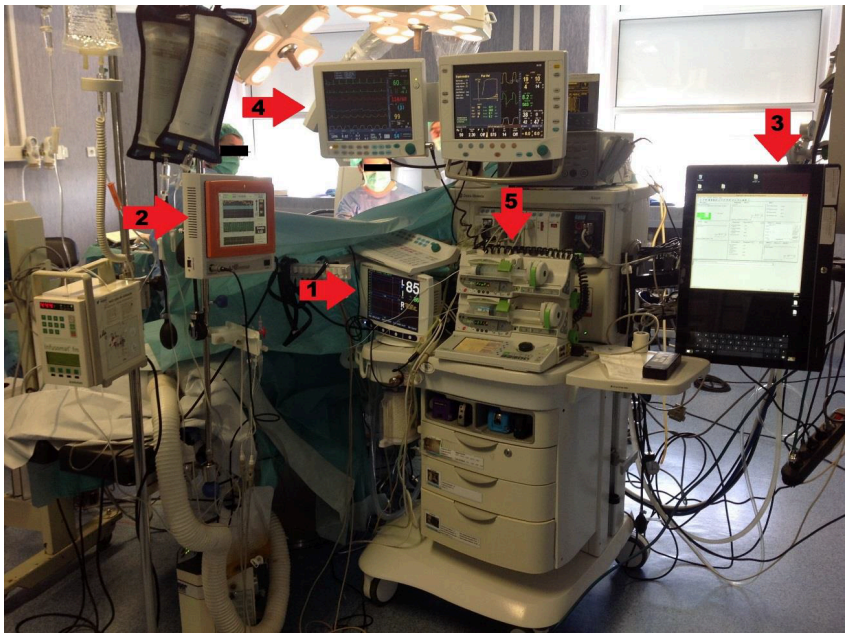


Figure 3.1 Monitors in the operating room: 1 – INVOS monitor, 2 – ANI monitor, 3 – Dedicated computer with Rugloop Software, 4 – Datex Ohmeda Aisys/GE monitor, 5 – TCI system (Fresenius Base Primea Orchestra).

Group 2

In the 141 patients of this group, induction started with a remifentanil Ce concentration of 2.5ng/mL [78] until plasmatic and effect-site concentration was balanced. Intravenous infusion of 1% propofol with Schnider's model[28] started at 3.3mL/kg/h until LOC, identified as lack of eye-opening to name-calling and tap on the forehead. Propofol Ce was set to a concentration lower than the Ce at LOC, through the application of a previously presented formula [80]. The moment of LOC and the 10 minutes after LOC were analyzed.

Group 3

In the 55 patients of this group, induction started with a 3ug/kg bolus of fentanyl. In patients whose Body Mass Index (BMI) was greater than 25, the dose of fentanyl of a 21.75 BMI was calculated. Three

minutes later, 30 mg of lidocaine was injected to avoid pain with propofol. Intravenous infusion of 1% of propofol [28] started at 3.3mL/kg/h until LOC, identified as lack of eye-opening to name-calling and tap on the forehead. The moment of LOC was rigorously recorded and propofol Ce was set to a concentration lower than the concentration at LOC. Until 10 minutes after LOC propofol Ce was not altered. The moment of LOC and the 10 minutes after LOC were the two endpoints analyzed in this phase.

Statistical analysis

The studied variables were: gender, age, height (cm), weight (kg), Body Mass Index (BMI), ASA classification, propofol Ce concentration at LOC (μg/mL), the volume of propofol until LOC (mL), remifentanil Ce at LOC (ng/mL), fentanyl Ce at LOC (ng/mL), BIS at LOC, EMG at LOC (μV), BP systolic at LOC (mmHg), HR at LOC (bpm), HR baseline (bpm), BP systolic at baseline (mmHg), percentage of BP systolic from LOC + 2 minutes to LOC + 10 minutes in relation to the baseline BP Systolic and product of HR per BP systolic (HRxBP systolic).

To test if the variables were normally distributed a Shapiro-Wilk test was used. For normally distributed variables, parametric tests were performed: To test for equality of variances Levene's test used and t-Student to test for equality of means. A 2-Way ANOVA test was performed to compare groups. Pearson and Spearman's tests were performed to test the correlation between different variables. A multivariate regression analysis was used to determine predictive factors for the propofol Ce concentration required for LOC. A p-value lower than 0.05 was considered statistically significant. SPSS version 22 and Excel version 2013 were used.

Results are presented as mean±standard deviation (SD) unless stated otherwise.

Results

Variability at the loss of consciousness

Table 3.1 shows demographics from patients in Group 1, Group 2, and Group 3.

There was a statistically significant difference between the three groups concerning age ($p=0.042$). There were no statistically significant differences between the three groups in relation to weight, height, BMI, gender, or ASA ($p>0.05$).

Table 3.2 presents the descriptive results for the studied variables about Group 1, 2, and 3. In Group 1 propofol Ce concentration at LOC was 5.19±0.97μg/mL, ranged from 2.73μg/mL to 7.40μg/mL. The infused volume of propofol until LOC was 11.92±2.85 mL, ranged from 6.76 mL to 24.22mL. In Group 2, propofol Ce concentration at LOC was 3.78±1.20μg/mL, ranged from 1.53μg/mL to 6.93μg/mL. The infused volume of propofol until LOC was 8.34±2.58mL, ranged from 3.83mL to 16.83mL. In Group 3, propofol Ce concentration at LOC was 3.87±1.51μg/mL, ranged from 1.37μg/mL to 7.25μg/mL. The infused volume of propofol until LOC was 8.37±3.09mL, ranged from 3.80mL to 16.77mL.

Table 3.1 Demographics from Group 1: induction performed with remifentanil and propofol; Group 2: induction performed with propofol and remifentanil; and Group 3: induction performed with fentanyl and propofol.

	Group 1	Group 2	Group 3
Age (yr.)	52 ± 14	53 ± 16	58 ± 12
Weight (kg)	70.47 ± 13.69	68.21 ± 12.71	67.53 ± 12.22
Height (cm)	163.60 ± 9.02	163.69 ± 12.26	163.44 ± 8.15
BMI (kg)	47.29 ± 6.19	46.31 ± 10.70	46.50 ± 5.64
Gender (Female / Male)	30 / 45	75 / 66	27 / 28
ASA (I / II / III)	28 / 35 / 22	21 / 52 / 17	13 / 32 / 10

Values are mean ± SD or number.

Groups 1 and 2 were compared because drugs used to perform induction were the same (Table 3.2). There were no significant differences between Group 1 and Group 2 for age, weight, height, BMI, and gender ($p>0.05$). Propofol Ce concentrations at LOC in Group 1 were significantly different from propofol Ce concentrations at LOC in Group 2 ($p<0.001$). Patients from Group 1 lost consciousness with higher propofol Ce concentrations than patients from Group 2. Similar results were found for the infused volume until LOC, remifentanil at LOC, BIS at LOC, and EMG at LOC.

Table 3.2 P values of Chi-square and student t-tests comparing the studied variables between Group 1 and Group 2.

Variables	Group 1 versus Group 2 p-value
Age (yr.)	0.796*
Weight (kg)	0.228*
Height (cm)	0.953*
BMI (kg)	0.453*
Gender (Female / Male)	0.683+
ASA (I / II / III)	<0.001+
Propofol Ce at LOC (μg/mL)	<0.001*
Volume of Propofol at LOC (mL)	<0.001*
Remifentanil Ce at LOC (ng/mL)	<0.001*
BP Systolic at LOC (mmHg)	0.847*
BIS at LOC	<0.001*
EMG at LOC (μV)	<0.001*
HR at LOC (bpm)	0.932*
BP Systolic at baseline (mmHg)	0.477*
HR at baseline (bpm)	0.357*
EMG at baseline (μV)	0.327*
% BP Systolic HR x BP	0.300*
HR x BP Systolic at LOC	0.946*

+Qui-square test; *Independent samples t-test.

Inter-patient variability (Figure 3.2 and Table 3.3) was calculated in two different manners for the three groups of patients: as the percentage ratio between the maximum and the minimum value, and as the percentage ratio between the maximum and the mean value. Results of the variability in Group 1, Group 2, and Group 3 related to the propofol Ce concentration at LOC, infused volume until LOC, BIS at LOC, and EMG at LOC are presented in Table 3.4.

Inter-patient variability of the propofol Ce concentration required for LOC, as the ratio between the maximum and the minimum value was 271%, 453% and 539% in patients from Group 1, 2, and 3, respectively. Inter-patient variability of the propofol Ce concentration required for LOC, as the ratio between the maximum and the mean value, was 142%, 183%, and 175% in patients from Group 1, 2, and 3, respectively. Inter-patient variability of propofol Ce concentration required for LOC was higher in Group 3.

Concerning the volume of propofol until LOC, variability was higher in Group 3 if calculated as the ratio between the maximum and the minimum values. The variability of BIS at LOC was higher in Group 2 when calculated as the ratio between maximum and minimum values. The variability of EMG at LOC was higher in Group 1.

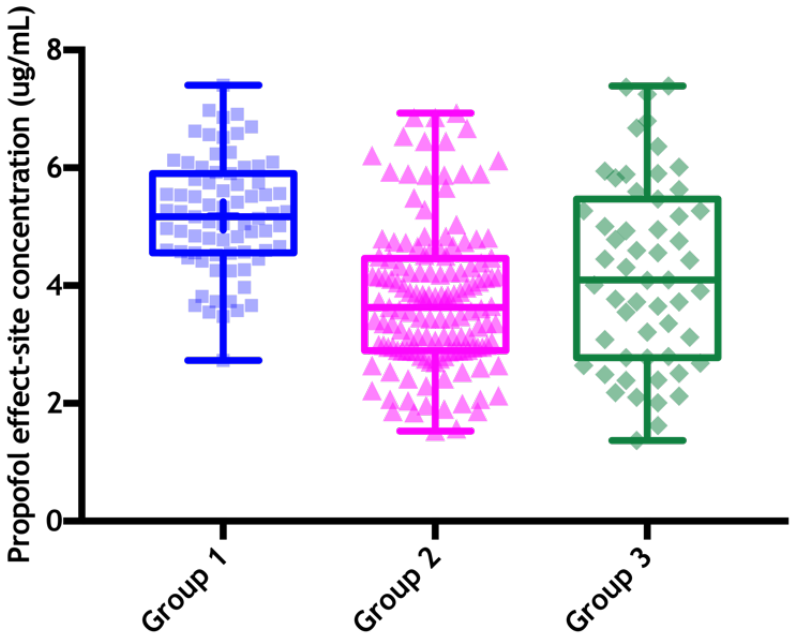


Figure 3.2 Box-plot diagram showing the propofol effect-site concentration at LOC in patients from Group 1, Group 2 and Group 3.

Multivariate analysis of predictive factors for propofol Ce concentration at LOC

Correlation analysis were scrutinized, among propofol Ce concentration at LOC, systolic blood pressure (BP Systolic) at LOC, heart rate (HR) at LOC, the product of HR and BP Systolic (HRxBP) at LOC, electromyography (EMG) at LOC, BIS at LOC, BP Systolic at baseline, HR at baseline, EMG at baseline, percentage of BP systolic from LOC+2 minutes to LOC+10 minutes about the BP baseline, patient's age, weight, height, gender, and BMI.

Table 3.3 Inter-patient variability of the propofol Ce concentration required for LOC and in the volume of propofol at LOC, BIS and EMG at LOC for Group 1, Group 2 and Group 3.

		Group 1	Group 2	Group 3
Propofol Ce at LOC (μg/mL)	Variability as the ratio between the maximum and the minimum value (%)	271.06	452.94	539.42
	Variability as the ratio between the maximum and the mean value (%)	142.58	183.33	174.70
Volume of Propofol at LOC (mL)	Variability as the ratio between the maximum and the minimum value (%)	358.28	439.42	441.31
	Variability as the ratio between the maximum and the mean value (%)	203.19	201.80	200.36
BIS at LOC	Variability as the ratio between the maximum and the minimum value (%)	197.27	288.88	208.19
	Variability as the ratio between the maximum and the mean value (%)	142.87	124.78	125.07
EMG at LOC	Variability as the ratio between the maximum and the minimum value (%)	350.38	184.44	153.34
	Variability as the ratio between the maximum and the mean value (%)	155.10	134.04	121.26

In all three groups of patients, the results revealed that there were positive and negative significant correlations between any two variables, which suggested that further analysis should be conducted. Multiple linear regression was calculated to predict propofol Ce concentrations at LOC based upon the studied variables. Preliminary analysis was performed to ensure there was no violation of the assumption of normality, linearity, and multicollinearity.

In Group 1, the following variables entered into the model: BP Systolic baseline and gender. A significant regression equation was found [$F(2, 71)=11.193$, $p<0.001$], with an R^2 of 0.240. Patients' predicted propofol Ce concentrations at LOC is equal to 5.052+0.010(BP Systolic baseline)-0.782(Gender), where BP Systolic baseline is measured as mmHg and gender, coded as 1=Male, 2=Female. Propofol Ce concentrations at LOC increased 0.010μg/mL for each mmHg of systolic blood pressure at baseline and males required 0.782 μg/mL more than females. Both BP Systolic at baseline and gender were significant predictors of propofol Ce concentrations at LOC.

In Group 2, the following variables entered into the model: percentage BP Systolic (%BP Systolic), gender, HR at LOC, BIS at LOC, and BP Systolic at baseline. A significant regression equation was found ($F (5, 123) =15.661$, $p<0.001=$, with an R^2 of 0.389. Patients' predicted propofol Ce concentrations at LOC is equal to 2.807-0.024(%BP Systolic)-0.965(Gender)+0.021(HR at LOC)-0.017(BIS at LOC)+0.013(BP Systolic at baseline), where %BP Systolic is measured as a percentage, gender-coded as 1=Male, 2=Female, HR at LOC measured as bpm and BP Systolic at baseline measured as mmHg. %BP Systolic, gender, HR and BIS at LOC, and BP Systolic at baseline were significant predictors of propofol Ce concentrations at LOC.

In Group 3, the following variables entered into the model: gender, BP Systolic at baseline, HR at LOC, HRxBP Systolic at LOC, BIS at LOC, %BP Systolic, BMI, BP Systolic at LOC, Weight, EMG at LOC, Age, EMG at baseline, HR at LOC and Height. A significant regression equation was found ($F (14, 38) =8.289$, $p<0.001=$, with an R^2 of 0.753. Patients' predicted propofol Ce concentrations at LOC is equal

to -9.530 - 1.423 (Gender) + 0.040 (BP Systolic at baseline) + 0.213 (HR at LOC) -0.001 (HRxBP Systolic at LOC)-0.036(BIS at LOC)+0.029(%BP Systolic)+0.142(BMI)+0.036(BP Systolic at LOC)-0.039(Weight)+0.022(EMG at LOC)+0.007(Age)+0.015(EMG at baseline) +0.213 (HR at LOC) +0.003(Height). Gender, BP Systolic at baseline, HR at LOC, HRxBP Systolic at LOC, BIS at LOC and %BP Systolic were significant predictors of propofol Ce concentrations at LOC.

Discussion and conclusions

Inter-patient variability in propofol requirements was analyzed in three different conditions, two by a retrospective analysis and one by a prospective study. In these three conditions, the amount of propofol required to produce unconsciousness varied widely between patients. Variability, calculated as the ratio between the maximum and the minimum value in percentage, was considered very high: more than 500% in the group with higher variability (Group 3). It is common to affirm that there is an important inter-patient variability in relation to the propofol requirements, however, as far as it is known, there are no studies quantifying variability so objectively or analyzing variability under such different conditions of anesthesia.

In clinical terms, by inducing anesthesia one can find patients who need an effect-site concentration of propofol to lose consciousness that varies in such a way that patients who need more propofol need more than 300% than those who need less propofol. Not only the variability was very high, but it also was similar in all three anesthesia protocols, demonstrating that the variability was independent of the type of opioid used in the induction or independent of if anesthesia started with propofol or with the opioid. Thus, this variability seems to be an intrinsic characteristic of propofol and may result from factors related to the pharmacokinetics and pharmacodynamics of propofol and not related to the context it was used to. Note that these variations were analyzed in effect-site concentrations, estimated with models that used age, gender, weight, and height. This means that the observed variability was independent of these variables, i.e., an elderly patient can lose consciousness with a lower or a higher concentration of propofol. The same occurred for different weights, heights or gender. So, before the induction of anesthesia, anesthesiologists should clearly identify the requirements of each individual patient. The recommended method of administering a specific amount of propofol based on a patient's weight and age should be replaced with a technique that allows individualization of the patient's needs. That means, administering propofol slowly at induction, and monitoring the patient's response continuously to precisely identify the moment of loss of consciousness, identifying the amount of propofol each patient requires, and then using that information to guide the infusion rate of propofol required to maintain an adequate level of anesthesia.

Gender and BP Systolic at baseline were the predictor factors that most influenced the propofol Ce concentrations at LOC. The results obtained showed patients with higher systolic blood pressures in the baseline, need more propofol requirements, probably because higher pressures correspond to a higher sensitivity to the hypnotic effects of propofol. Results also showed that males need more propofol to lose consciousness than females. Published studies regarding this issue are contradictory [81][82]. In the study from Haensch et al. [81] women needed a higher effect-site concentration of propofol to lose consciousness

than men. In the study of Graça et al. [82], they may have obtained those results because men were significantly older than women. In accordance with these results are the ones obtained by Kodaka et al. [83].

In the current study, one found that effect-site concentrations of propofol required for LOC were lower when the opioid was administered before induction, which is probably due to the hypnotic effects of opioids such as remifentanil [84]. A previous study showed that propofol concentration required for LOC was reduced with the increase of fentanyl concentration [85]. Similar results were found in the current study, the use of fentanyl in Group 3 influenced and decreased the propofol Ce concentration at LOC.

The variability of BIS was much lower in the group that started infusion with propofol followed by remifentanil after LOC. This was probably due to the lower effect-site concentration of propofol and the fact that the BIS monitor is based on propofol. In fact, the BIS may not correctly foresee the anesthetic depth when an opioid is included in the induction, either because it does not capture the hypnotic effect of the opioid or because the propofol Ce is greater if anesthesia is induced without an opioid [60].

In relation to the predictive factors, it is important to mention that the results of the prospective study were much more credible once the data from the retrospective studies were not collected with this specific goal. Even so, it was interesting to analyze these results, since the induction without opioid was different and the heart rate and blood arterial pressure assumed a more important role. In addition, demographic variables demonstrated more predictive of propofol effect-site concentrations required for LOC than physiological variables. This may be due to the fact that the pharmacokinetic model was not ideal, or because this model did not contemplate well variables such as age, gender, weight, and height. It is also believed, after analyzing the results, that if the ASA score were a criterion provided by the pharmacokinetic model, the calculated concentrations would probably be closer to the real value.

On the basis of the results of the present study, one can conclude that there was a widely inter-patient variability in propofol effect-site concentrations to induce loss of consciousness, regardless of whether the induction method was started with propofol, remifentanil or fentanyl. This variability is clinically very relevant because of its magnitude and because of the consequences that excessive propofol concentrations represent. There was a higher variability in relation to the median patient of the population, which at the moment is the only way to anticipate the propofol effect-site concentration to induce loss of consciousness. To note that these variations were analyzed in effect-site concentrations, calculated according to age, gender, weight, and height, which suggests that at least the Schnider's pharmacokinetic model does not contemplate well or is not well adjusted to these variables. This led us to the need for conducting future studies to analyze age, gender, weight, and height, understand how they influence models, and improve pharmacokinetic models by adding more variables. To better assess the prediction with the Schnider model in the studied patients, it would be very important to analyze the concentration of propofol measured in the plasma. Unfortunately, it was not possible to do this analysis in a useful time.

Other similar studies should be conducted, with a larger sample of patients, to be possible to identify more accurately the predictive factor of propofol effect-site concentration at LOC.

From a clinical point of view, the question of inter-patient variability must be overcome by using an induction technique that allows the individualization of a patient's needs.

The most important achievement of this study was the understanding that induction must be performed in anticipation of a very wide inter-patient variability and that one may use methods to accurately identify the requirements of each patient.

Table 3.4 Descriptive statistics for the studied variables in Group 1, Group 2 and Group 3.

	Mean (95% CI)	Standard Deviation	Minimum	Maximum	Median (Interquartile Range)
Propofol Ce at LOC (μg/mL)					
Group 1	5.19 (4.96-5.41)	0.97	2.73	7.40	5.23 (1.34)
Group 2	3.78 (3.57-3.99)	1.20	1.53	6.93	3.65 (1.47)
Group 3	4.23 (3.80–4.66)	1.58	1.37	7.39	4.10 (2.69)
Volume of Propofol at LOC (mL)					
Group 1	11.92 (11.26-12.59)	2.85	6.76	24.22	11.52 (3.48)
Group 2	8.34 (7.90-8.79)	2.58	3.83	16.83	7.77 (3.21)
Group 3	8.37 (7.18–9.57)	3.09	3.80	16.77	7.85 (4.84)
Remifentanil Ce at LOC (ng/mL)					
Group 1	-	-	-	-	-
Group 2	2.49 (2.43-2.55)	0.32	0.57	3	2.51 (0.03)
Group 3	-	-	-	-	-
Fentanyl Ce at LOC (ng/mL)					
Group 1	-	-	-	-	-
Group 2	-	-	-	-	-

Group 3	3.36 (3.18–3.54)	0.47	2.70	4.50	3.30 (0.67)
BP Systolic at LOC (mmHg)					
Group 1	124.63 (119.56-129.70)	21.74	77.67	200	122.95 (27.50)
Group 2	124.92 (121.58-128.26)	19.25	84.22	196.96	123.33 (22.30)
Group 3	130.29 (122.10- 138.47)	21.11	100.30	171.03	125.25 (35.24)
HR at LOC (bpm)					
Group 1	69.32 (66.61-72.03)	11.62	45.00	107.67	68.00 (13.17)
Group 2	69.75 (66.82-72.67)	16.84	45.00	167.33	68.00 (16.08)
Group 3	65.06 (60.35-69.77)	12.14	45.33	97.67	63.33 (9.92)
HR x BP Systolic at LOC					
Group 1	8616.96 (8159.89-9074.04)	1959.02	3650.35	15001.57	8280.00 (2187.98)
Group 2	8722.91 (8296.98-9148.85)	2464.17	3789.76	18908.63	8345.96 (2850.30)
Group 3	8493.63 (7625.53-9361.72)	2238.75	5532.24	15704.58	8062.78 (2898.18)
EMG at LOC (μV)					
Group 1	40 (38.58-41.41)	6.07	28.97	57.15	39.08 (8.92)
Group 2	43.77 (42.74-44.80)	5.91	31.81	58.67	43.00 (10.35)
Group 3	44.26 (42.18-46.34)	5.37	35.00	53.67	45.00 (7.66)
BIS at LOC					
Group 1	62.28 (58.57-66)	15.93	27.57	96.60	63.33 (25.50)

Group 2	76.40 (74.13-78.68)	13.11	33.00	95.33	80.53 (12.48)
Group 3	74.36 (68.78-79.93)	14.38	44.67	93.00	78.16 (22.5)
BP Systolic at baseline (mmHg)					
Group 1	141.17 (136.04-146.30)	21.99	108	200.00	140.00 (32.61)
Group 2	138.53 (135.25-141.81)	18.89	82.29	193.00	137.57 (18.07)
Group 3	144.11 (135.20-153.03)	22.99	109.53	185.28	144.42 (38.13)
HR at baseline (bpm)					
Group 1	70.89 (67.69-74.09)	13.72	44.00	121.67	71.33 (19.67)
Group 2	72.87 (70.49-75.25)	13.72	44.67	114.33	70.00 (18.17)
Group 3	71.81 (64.25-79.37)	19.49	52.00	141.33	66.83 (21.67)
EMG at baseline (μV)					
Group 1	48.39 (47.17-49.62)	5.26	36.87	58.91	47.44 (7.46)
Group 2	49.04 (48.04-50.04)	5.76	34.74	67.02	48.24 (6.72)
Group 3	49.69 (47.13-52.25)	6.60	39.67	61.67	47.83 (12.68)
% BP Systolic					
Group 1	-15.75 (-18.55-(-12.95))	12.16	-42.80	21.83	-15.60 (16.32)
Group 2	-17.72 (-20.03-(-15.41))	13.73	-49.74	43.40	-20.91 (19.31)
Group 3	-21.96 (-28.10-(-15.83))	15.82	-51.36	5.95	-18.11 (24.10)

3.2 Evaluation of Bispectral Index time delay in response to anesthesia induction: an observational study

Ana Leitão Ferreira MSc, Joaquim Gabriel Mendes PhD, Catarina Nunes PhD, Pedro Amorim MD

Abstract

Background and Objectives: According to the manufacturer the Bispectral Index has a processing time delay of 5 to 10 seconds. Studies addressing this have suggested longer delays. It was evaluated the time delay in the Bispectral index response.

Methods: Based on clinical data from 45 patients, using the difference between the predicted and the real Bispectral Index, calculated during a fixed 3 minutes period after the moment the Bispectral Index dropped below 80 during the induction of general anesthesia with propofol and remifentanil.

Results: The difference between the predicted and the real Bispectral Index was on average 30.09 ± 18.73 seconds.

Conclusion: Results may be another indication that the delay in Bispectral index processing may be much longer than stated by the manufacture, a fact with clinical implications.

Keywords: Bispectral Index Monitor, Depth of Anesthesia, Awareness, Time Delay.

Introduction

The Bispectral Index™ (BIS; Aspect Medical Systems Inc., Newton, MA) is a useful tool to assess the adequacy of the level of hypnosis during general anesthesia, although limitations were described [86][87]. The BIS index is derived utilizing a composite of measures from components of quantitative electroencephalogram (EEG) signal processed using bispectral, power spectral, and time-domain analysis [88][89][90]. These measures were combined via an algorithm to optimize the correlation between the EEG and the clinical effects of anesthesia, and quantified using the BIS index range [88][89][90]. This algorithm is proprietary, meaning that it is known only by the manufacturer and was never disclosed. The final result is a numerical index ranging from 0 to 100, with 0 being the value associated with the EEG isoelectric (flat) and 99 to the brain activity of a patient awake and alert.

The BIS index has a processing time delay, which, according to the manufacturer is a delay of approximately 5 to 10 seconds [88]. However, these values have been disputed. Anecdotal reports have shown that cutting off the BIS sensor with a scissor so that the BIS four-electrodes sensor remains attached to the forehead but no longer communicating with the monitor, resulted in the monitor displaying a BIS value for longer than 10 seconds. This was shown in an educational video posted online by the Washington University in Saint Louis [91]. This video received wide attention and was used by BIS detractors to question its accuracy [92]. A more accurate evaluation of a possible time delay in BIS processing was done in studies using processed EEG that was fed to the depth of anesthesia monitors. Two studies using this method reported BIS delays as long as 66 seconds [93][94].

In a previous work [95], it was identified a time delay between BIS signal and modeled BIS of approximately 120 seconds. In this study, the modeled BIS was obtained accordingly to an interaction model structure [96] which relates the BIS values (drug effect) to the effect-site concentrations of propofol and remifentanil. The time delay was calculated using the difference between BIS signal and modeled BIS in a random value of BIS. It was concluded that the time delay depends not only on the dynamics of the patient but may also be influenced by the BIS processing time delay, which was proven to vary [93].

The present study was to evaluate the time delay in the BIS response, based on clinical data from 45 patients, using the difference between the predicted and the actual BIS, calculated during a fixed 3 minutes period after the moment the BIS dropped below 80 during the induction of general anesthesia with propofol and remifentanil.

Methods

Under institutional review board approval and written informed consent, consecutive adult patients undergoing routine neurosurgical procedures were anesthetized as described below. Exclusion criteria were any alterations in mental status or BIS < 90 before induction, significant cardiovascular, renal, hepatic, or respiratory pathology, and obesity (BMI>35kg/m2). Procedures done by the same anesthesiologist over five months were included.

A. Data acquisition protocol

In the operating room, after arrival, patients were monitored with an electrocardiogram (ECG), noninvasive blood pressure (BP), oxygen saturation via pulse oximetry (SpO_2), and BIS. After placement

of standard monitors and placement of an intravenous line in the dorsum of the hand, an infusion of an equilibrated electrolytic solution was started at 400 mL/h and infused at this rate through the entire surgery. Patients were pre-oxygenated with 100% O_2 for three minutes. Clinical practice for neurosurgical procedures consists of opioid-propofol anesthesia using a TCI system. Anesthesia began with the administration of 1% propofol at 200 mL/h using an infusion pump (Asena Alaris GH). Once propofol reached the venous catheter, the tourniquet was released. The level of consciousness was assessed every 10 seconds using the Observer's Assessment of Alertness/Sedation Scale (OAA/S) [36].

At the loss of consciousness (LOC), which was defined as loss of eye-opening in response to name-calling repeatedly in a loud voice, i.e., a score of 3 in the OAA/S, the propofol effect-site target was set to the individual effect-site concentration at which LOC occurred, and remifentanil infusion started (Asena Alaris TIVA) with an initial plasma target of 2.5 ng/mL and titrated during surgery (Figure 3.3). Manual ventilation was started, rocuronium was then administered at 0.6 mg/kg. Laryngoscopy and intubation were performed and the drug's infusion was changed according to the patient's need to maintain a target range for BIS (45–60), mean arterial pressure, and heart rate within ±30% of the respective baseline values.

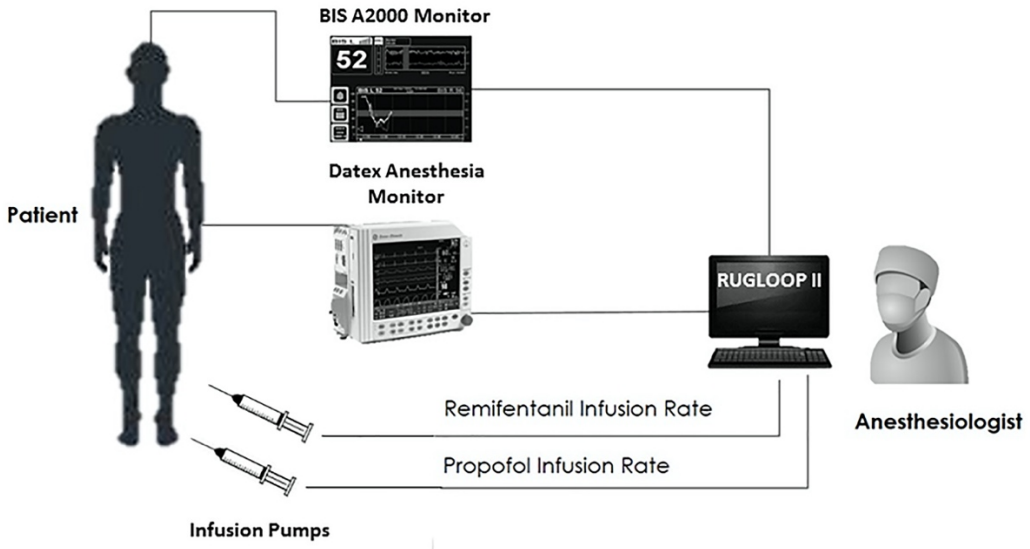


Figure 3.3 Anesthesia setup.

B. Bispectral index modeling

Patients were monitored with an A-2000XP BIS monitor (Aspect Medical Systems, Newton, MA) using a BIS-Sensor (Aspect Medical Systems) placed according to the instructions of the manufacturer on the forehead, and an AS3 Datex monitor (Datex-Engstrom, Helsinki, Finland) connected by RS-232 interface to a PC using Rugloop II software (DEMED, Temse, Belgium) for data capture at 5-second intervals. Rugloop II (via RS-232 interface) was used to control the propofol and the remifentanil infusion pump and to record the data. Along with the BIS response, the infusion rate of propofol and remifentanil were recorded.

In order to model the BIS response, the drug effect itself has also to be modeled. This way, the drug behavior in the human body was modeled considering three phases: pharmacokinetic phase (infused dose

to plasma concentration), pharmacodynamic phase (plasma concentration to effect-site concentration), and finally translation between effect-site concentration and measurable effect (BIS). The overall model structure is shown in the block diagram from Figure 3.4. The infusion rates were used to calculate the plasma and effect concentration of both drugs using two PK-PD models. For propofol, the PK-PD parameters from Schnider [28] were used, whereas for remifentanil the parameters from Minto [29][78] were employed. Bruhn et al. [97] presented an interaction model structure to relate the EEG parameter values (including BIS) to the effect-site concentrations of propofol and remifentanil.

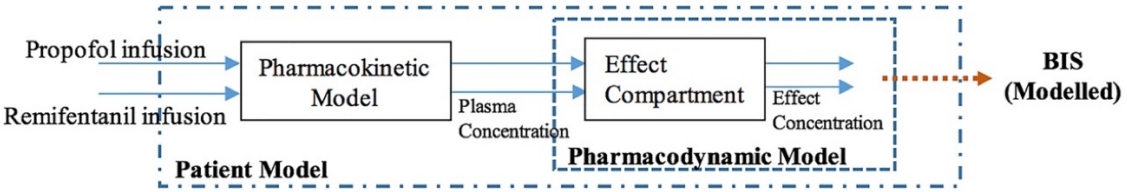


Figure 3.4 Block diagram of BIS modulation.

C. BIS time delay calculation

The BIS time delay for each patient was calculated as the average of the differences between the predicted response of the pharmacodynamic model and the actual BIS signal of the patient, measured from the first time the BIS signal dropped below 80 until the moment both signals intersect (case 1). In the first step of the surgical procedure, only propofol is administered, associating a characteristic decrement in the modeled BIS function. At the time the propofol infusion stops and the remifentanil begins, the modeled BIS changes its behavior to fit the interaction between both drugs. A BIS value of 80 is a standard threshold where the hypnotic effect has clearly started but the patient is still conscious.

For the cases where an interception did not occur (case 2), the endpoint was defined as 5 minutes after the beginning of anesthesia induction. This time limit was selected to be an instant prior maintenance phase, in which the real BIS value is stable.

Also considered were the cases where both, modeled and real BIS, almost overlap (case 3).

D. Data Analysis

A sample size calculation was performed considering the results previously obtained (time delay 0.63±0.28 minutes) [95] versus the BIS monitor processing time delay of 10 seconds (or 0.17 minutes), with 95% power, α=0.1 (Sample size paired *t*-test, StatsDirect V3). A minimum sample size of 41 pairs/patients was obtained. Considering a 10% exclusion rate, a final sample size of 45 patients was established.

Data distribution is expressed as mean ± SD. Statistical analyses were performed using MATLAB 2014a (MathWorks, Inc., Natick, MA) and IBM SPSS Statistics (IBM Corporation, NY). A *p* lower than 0.05 was considered statistically significant.

Results

A total of 45 neurosurgical patients were included in this study. Demographics for all 45 patients were: 51±15 years of age (minimum and maximum, 20 and 79 years old, respectively), 70±13 kg, 163±9 cm, 17 males and 28 females.

Propofol and remifentanil effect-site concentrations for each patient during the first 15 minutes at the induction of anesthesia are illustrated in Figure 3.5a). Loss of consciousness represented as the time when remifentanil has started to be administered occurred within 15 minutes in all patients.

The BIS values captured from the Rugloop software and the BIS values modeled for each patient during the first 15 minutes at the induction of anesthesia are presented in Figure 3.5b). There is a time delay between the real BIS signal and the modeled BIS, i.e. the model predicts the BIS responses earlier than it really is.

Figure 3.6 represents the BIS time delay (Δt) of four different patients. As observable from the comparative behavior of the real and the modeled BIS there are three major groups of results in this study. The majority of the registered cases (n=40) fit as Figure 3.6a) and Figure 3.6d) where the signals intercept. In Figure 3.6b) is presented the data of a patient in which real and modeled BIS signal did no intersect. There were 5 cases in total. In the cases similar to Figure 3.6c), modeled and real BIS almost overlap (n=2), resulting in almost no time delay (in general lower than 5 seconds).

Figure 3.7 represents the BIS time delay between the BIS signal and the predicted BIS for each patient.

Time delays were 30.09 ± 18.73 seconds (0.50 ± 0.31 minutes) and there are only 2 cases where the delay is in fact less than 10 seconds apart, 4.7 and 5.3 seconds, for patients 22 and 25, respectively.

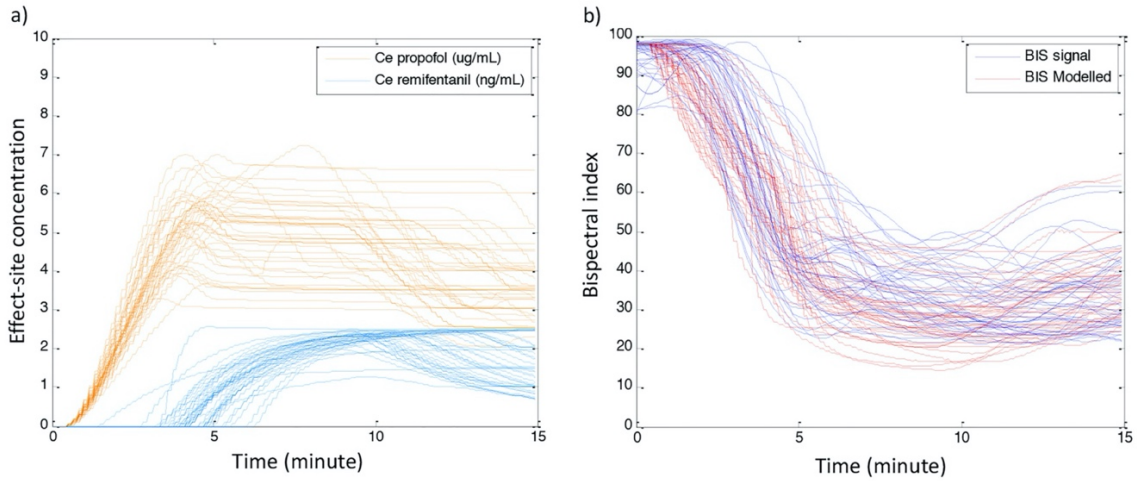


Figure 3.5 Data results from all 45 patients: a) Effect-site concentration of propofol and remifentanil for each patient during the first 15 min of anesthesia induction; b) Real versus modeled BIS values.

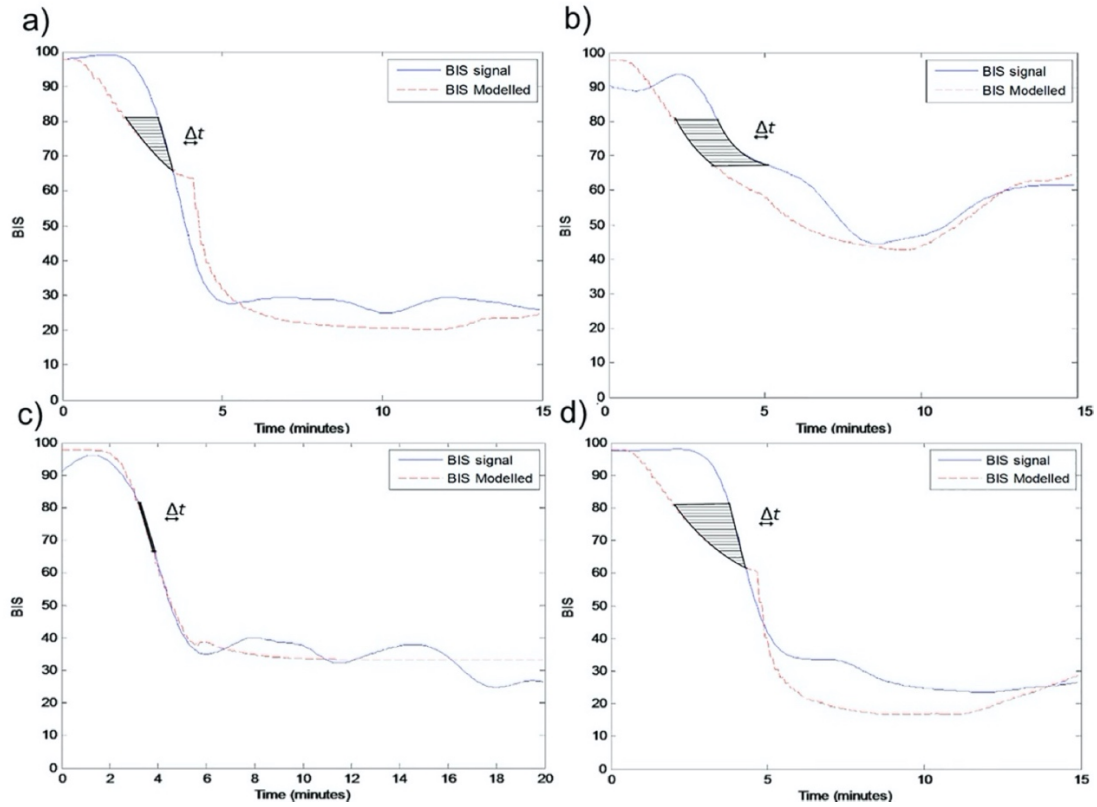


Figure 3.6 Time delay (Δt) between the real and the modeled BIS for: a) patient #5, b) patient #19, c) patient #22 and d) patient #27.

Discussion

All but one of the currently approved depth-of-anesthesia monitors use EEG derived indexes [98]. Since the EEG is a complex signal, the calculation of a derived index after the processed analysis is time-consuming, resulting in some processing time delay. Clinically, the existence of such a delay is relevant. BIS monitor adds a variable time delay to display the BIS index value, which was suggested, in this study, as 30.09 ± 18.73 seconds. This time delay was calculated from the data of 45 patients aged between 20 and 79 years old. Purdon et al. [99] described significant age-dependent changes in the characteristics of the effects of anesthesia on the EEG with increasing age. However, the BIS index value from the BIS monitor is validated for clinical use regardless of age. Additionally, there is no existence, neither on the manufacturer nor on literature, of indications that the EEG-based index is influenced by age.

The importance of a potential BIS index time delay can be demonstrated by the fact that, for example, a noxious stimulation skin incision could arouse a patient under general anesthesia, whereas the depth of anesthesia monitors could continue to show a value consistent with appropriate anesthesia. The moment the anesthesiologist was alerted by a rise in the index value, the patient could have already suffered pain and psychological trauma, resulting in a case of intra-operative awareness. Awareness under general anesthesia, although infrequent, is of significant concern to patients. It can be devastating and associated with posttraumatic stress disorders [100][101]. The BIS index was initially introduced, aiming at preventing awareness and its efficacy at doing it was demonstrated [102][103]. It is not known how much time with a BIS value above 60 is necessary for awareness to occur, but it has been claimed that at least 5 minutes with

a BIS above 60 is necessary to create awareness with recall [102][104]. Interestingly, one large randomized trial performed to assess BIS in preventing awareness reported two patients who developed awareness [102]. A BIS reading higher than 60 occurred in both cases, lasting for 5 and 9 minutes, respectively [102]. Given this data, it seems quite unlikely that the possible time delay suggested by the results (30.09 ± 18.73 seconds) would be sufficient to create awareness with recall. However, one cannot be sure of this, and ideally, the depth of anesthesia monitors should have no delay at all.

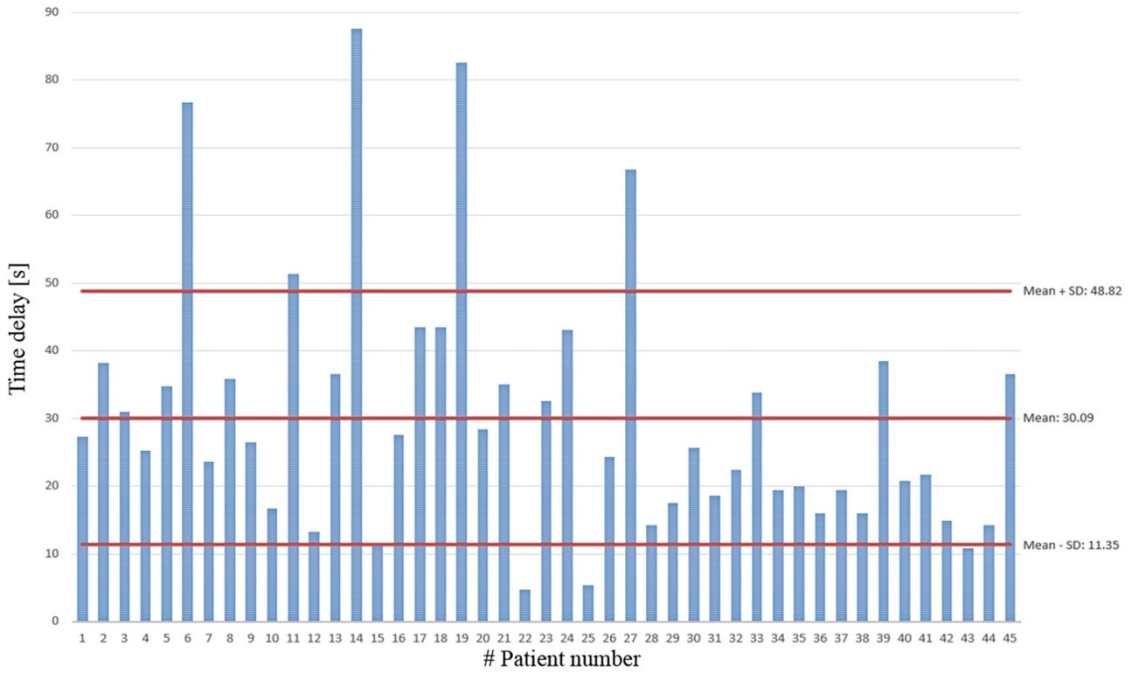


Figure 3.7 Time delay (Δt) between the real and the modeled BIS for all patients.

If a delay in displaying a high BIS value above 60 could increase the risk of awareness, a delay in displaying a low BIS value below 45, could also have clinical implications. Patients with at least 5 minutes with BIS value below 40 had a hazard ratio for death of 1.41 within four years of follow-up compared to patients whose BIS was always above 40 [105]. Also, cumulative time with a BIS value below 45 was shown to be independently associated with mortality at one year following surgery [106][23]. Therefore, it can be hypothesized that cumulative periods with undetected BIS below 45 or 40 could adversely impact on the patient's outcome. That could indeed happen due to summing up several periods with undetected low BIS due to a time delay in BIS processing.

Therefore, the clinician must be informed about the exact delay in the processing time of anesthesia indexes' depth. There has always been an interest among the anesthesiology research community to investigate the time delay for different monitors. However, few studies were performed trying to measure the processing time delay objectively. The reason is that it is not easy to implement a tool or to design a method capable of accurately measuring the delay. In the study performed by Pilge et al. [94] using artificially generated EEG signals, the time delay to detect the transition from "general anesthesia" to "awake" was 30 seconds, with some cases showing a delay as long as 66 seconds (for decreasing index values). The fastest response in BIS was seen in the transition between "awake" (BIS 98) to "general

anesthesia" (BIS 52) with a delay of 14 seconds [94]. This study has received criticism because it analyzed computer-generated EEG signals and not real raw EEG signals. A subsequent study from the same investigators tried to overcome that criticism by analyzing real EEG recorded from patients subjected to anesthesia [93]. The calculated delay for the BIS was identical to the sixty seconds reported in the first study. Simulating a sudden wake-up reaction by changing the input signal from "general anesthesia" to "awake BIS" showed a delay of 25 seconds [93]. Both studies from these authors also examined the processing delay of other monitors, finding processing time delays for the Cerebral State® monitor (Danmeter, Odense, Denmark) and the Narcotrend® monitor (version 4.0, MonitorTechnik, Bad Bramstedt, Germany).

The results from the actual study suggest the existence of a delay in processing the BIS index longer than that stated by the manufacture but in agreement with the results from previous studies addressing this delay [93][94][95]. Results also highlight the importance of relying on observing the EEG waves that are displayed in real-time. In addition, one should state that the suggested time delay may be related to the fact that the pharmacokinetic model (ke_0) does not correctly predict the effect/concentration delay or due to the inter-patient variability, which can be greater than expected.

Further investigation to find the influence of the suppression rate in the time BIS delay also deserves an in-depth study. Also, one should be evaluating the effect of altering the ke0 of the PK-PD model to 0.21 in the estimation of the effect-site target and the plasma concentrations. Additionally, the time delay in other measurable effects such as the State Entropy (SE) of the EEG can give complementary information.

3.3 Neuro-fuzzy models to predict the required propofol amount for loss of consciousness during general anesthesia: a preliminary study

Ana Leitão Ferreira MSC, Joaquim Gabriel Mendes PhD, Pedro Amorim MD, Catarina Nunes PhD

Abstract

This study presents several models to predict the total amount of the anesthetic drug propofol until the moment of loss of consciousness during the induction phase of anesthesia, considering different clinical variables. Data from 49 patients under anesthesia for neurosurgical procedures was used. Takagi-Sugeno-Kang (TSK) fuzzy models were used to describe the effect of clinical variables on the amount of propofol required for loss of consciousness. The parameters of the TSK models were optimized using an Adaptive Network-Fuzzy Interference System. All models were trained with the data of 35 patients and tested with the data of 14 patients. These models proved to have reasonable prediction properties. The best-balanced performance was achieved with only two inputs given to the fuzzy model, related to the blood systolic pressure and the Bispectral Index of the EEG.

Keywords: personalized anesthesia; loss of consciousness; fuzzy logic; ANFIS.

Introduction

In clinical practice, anesthesiologists use a combination of anesthetic drugs for surgery, including the most commonly used propofol, to render the patient unconscious. In a previously published work [107][20], one determined that the amount of propofol required to induce Loss Of Consciousness (LOC) varied widely between patients (≈300 %) and that more than two-thirds of the patients needed less than the initial dose recommended by the drug package inserts.

Precisely identifying of the moment of LOC during the induction phase of general anesthesia is of extreme importance for determining the amount of propofol each patient requires and then using that information to guide the drug infusion rate required to maintain an adequate level of anesthesia throughout the surgery.

Currently, methods to decide the LOC's exact moment are still based on subjective analysis [36]. Objectively, there is depth of anesthesia monitors, such as the Bispectral Index (BIS) (Aspect Medical System, Newton, MA, USA), which allow the maintenance of a steady-state during surgery. However, it does not allow the determination of LOC's instant, which remains as an open issue. After acquiring a new data-set, BIS evaluation is characterized by a delay, which can even reach one minute [88][95]. The anesthesiologists should be aware of situations that cause false BIS readings to avoid complications, such as awareness [11][21] or excessive anesthesia.

From a clinical practice point of view, it would be beneficial to predict the moment of LOC. The objective of this study was to estimate the total amount of propofol required to achieve LOC (volume in ml), using clinical data gathered during anesthesia induction. Only variables measured and available in everyday standard clinical practice were used.

In this study, different Takagi-Sugeno-Kang (TSK) fuzzy models were developed to predict the amount of propofol a patient requires for LOC. Statistical correlation analysis was performed to determine the clinical variables related to the propofol volume. An Adaptive Network-Fuzzy Interference System (ANFIS) was used to optimize the model parameters. The obtained TSK model was trained with clinical data obtained from 35 patients and tested with 14 patients' data. If the amount of propofol can be estimated, then the time to achieve LOC can be also predicted.

Methods

A. Clinical Data

Data collected during 49 neurosurgical interventions (with local ethical committee approval) were used to model a typical patient's LOC, using the infused propofol volume. This data was acquired from an internal clinical database and utilized retrospectively. The level of depth of anesthesia was manually controlled by the anesthesiologist using as reference the patient's vital signs and BIS monitor. The following clinical signs were recorded every 5 seconds: Heart Rate (HR), Systolic Arterial Pressure (SAP), BIS, Electromyography (EMG), and infused volume of propofol.

Baseline values were recorded at the moment the propofol infusion started. The 49 patients studied were 53±15 years, 70±13 kg, 163±8 cm, 18 males. The data from 35 patients were used to develop the prediction model, and the data from the remaining 14 patients were used for testing.

B. Fuzzy Models

A fuzzy TSK model [108] was used for predicting the total infused volume of propofol until LOC. The TSK fuzzy system is constructed from the following rules:

$$If\ x_1\ is\ C_1^l\ and\ \dots and\ x_n\ is\ C_n^l\ then \\ y^l = c_0^l + c_1^l x_1 + \cdots + c_n^l x_n \tag{1}$$

where C_i^l are fuzzy sets, c_i^l are constants, and $l = 1, \dots\ m$. That is, the antecedent parts of the rules are the same as in the ordinary fuzzy "If-then" rules, but the consequent parts are linear combinations of the input variables. Given an input $x = (x_1, \dots, x_n)\ \in U\ \subset\ R^n$, the output $f(x) \in V\ \subset\ R$ of the TSK fuzzy model is computed as the weighted average of the $y^{l'}s$, (2).

$$f(x) = \frac{\sum_{l=1}^{m} y^l w^l}{\sum_{l=1}^{m} w^l}$$

$$w^l = \prod_{i=1}^{n} \mu_{C_i^l}(x_i)$$

where $\mu_{C_i^l}(x_i)$ is the membership function of x_i in the fuzzy set C_i^l. The ANFIS identifies a set of parameters through a hybrid learning rule combining the back-propagation gradient-descent and the least-squares method. This was used to determine the parameters for the fuzzy TSK model [109]. The ANFIS system was built through the fuzzy toolbox available for Matlab2017b. The following properties were used for the models: a grid partition or subtractive clustering on the training data to generate the initial Fuzzy Interference System (FIS) structure, Gaussian input membership functions, and hybrid optimization method.

Results

The results are the correlation analysis in the search for informative variables concerning the total infused volume of propofol until LOC and the fuzzy TSK models' structure and outcomes. The data were divided into training and testing data sets. These sets are constituted by the data of 35 and 14 patients, respectively.

A. Correlation Analysis

A set of clinical variables were analyzed for correlation with the total infused volume of propofol until LOC. Table 3.5 shows the correlation coefficients for: patient age, patient Lean Body Mass (LBM), percentage of HR at LOC in relation to the baseline (% HR), percentage of SAP at LOC in relation to the baseline (% SAP), percentage of BIS at LOC in relation to the baseline (% BIS) and percentage of EMG

at LOC in relation to the baseline (% EMG). These clinical variables were chosen because they represent the patient's parameters and influence the drug distribution. All analyzed variables are available to the anesthesiologist before LOC and can be used to predict.

Table 3.5 Correlation coefficients between clinical variables at LOC and the total infused volume of propofol until LOC.

Variable	Correlation coefficient	Statistical *p*-value
Age	0.006	0.966
Lean body mass (LBM)	0.092	0.530
% Heart rate (HR)	0.124	0.400
% Systolic arterial pressure (SAP)	0.435	0.002
% BIS	0.314	0.028
% EMG	0.168	0.249

Analyzing Table 3.5 shows that the % SAP and the % BIS had a correlation coefficient with statistical significance ($p<0.05$).

B. Fuzzy Models

Seven different sets of the clinical variables evaluated for statistical correlation were used as inputs to TSK fuzzy models to estimate the infusion volume of propofol at LOC. Not only the variables with significant correlation coefficients were used since the TSK models trained by ANFIS are more powerful for data fitting and may productively use extra information. In addition, variables may have a nonlinear correlation. The TSK models were named according to the input set used: Fuzzy Model 1 uses as inputs the % SAP and % BIS; Fuzzy Model 2 uses Age, LBM, % SAP and % BIS; Fuzzy Model 3 uses Age, LBM, % SAP and % BIS; Fuzzy Model 4 uses % HR, % SAP, % BIS, and % EMG; Fuzzy Model 5 used Age, % HR, % SAP, % BIS and % EMG, Fuzzy Model 6 uses Age, LBM, % HR, % SAP, % BIS and % EMG and finally, Fuzzy Model 7 uses % HR and % SAP.

The initial FIS used by ANFIS is generated using grid partition according to the specific number of membership functions. All the membership functions are Gaussian. A number of 3 and 5 membership functions for each input were tested. In addition, subtractive clustering was used to determine the input membership functions. The ANFIS was able to optimize the parameters for all the fuzzy TSK models. Table 3.6 shows the mean absolute error for Fuzzy Models 1 to Fuzzy Model 7, considering the training and testing data sets.

The best performance was achieved for Fuzzy Model 1 with 25 rules (grid partition), Fuzzy Model 1 with 4 rules (subtractive clustering), Fuzzy Model 4 with 34 rules (subtractive clustering) and Fuzzy Model 1 with 17 rules (subtractive clustering). The test error variability for these models is presented in Figure 3.8, and testing errors of these models are not statistically different (ANOVA p=0.867).

Table 3.6 Mean absolute error for the fuzzy models for the total infused volume until LOC for the training and testing data sets. *Using grid partition; +Using subtracting clustering.

Model	Structure	Training data set	Testing data set
Fuzzy Model 1	9 rules*	0.29	4.79
	25 rules*	2.26e-4	2.93
	4 rules+	0.97	3.06
	8 rules+	0.02	4.39
	17 rules+	8.11e-5	3.92
Fuzzy Model 2	27 rules*	9.20e-5	4.29
	6 rules+	2.60e-4	7.16
	10 rules+	1.20e-4	5.17
	33 rules+	2.91e-6	4.59
Fuzzy Model 3	81 rules*	1.47e-6	7.23
	3 rules+	0.65	5.85
	11 rules+	3.35e-5	5.93
	19 rules+	3.52e-6	5.37
Fuzzy Model 4	81 rules*	2.43e-5	4.18
	7 rules+	4.08e-4	4.05
	14 rules+	2.30e-5	4.26
	34 rules+	6.24e-6	3.21
Fuzzy Model 5	243 rules*	1.20e-6	5.13
	6 rules+	4.51e-4	8.02
	13 rules+	8.61e-6	4.63
	32 rules+	5.44e-6	4.18
Fuzzy Model 6	64 rules*	4.93e-7	5.82
	7 rules+	2.85e-5	4.45
	15 rules+	2.02e-6	4.81
	25 rules+	7.17e-6	4.08
Fuzzy Model 7	9 rules*	0.56	44.50
	25 rules*	3.20e-4	6.02
	6 rules+	0.44	26.50
	10 rules+	0.09	22.32
	17 rules+	3.40e-4e-5	6.14

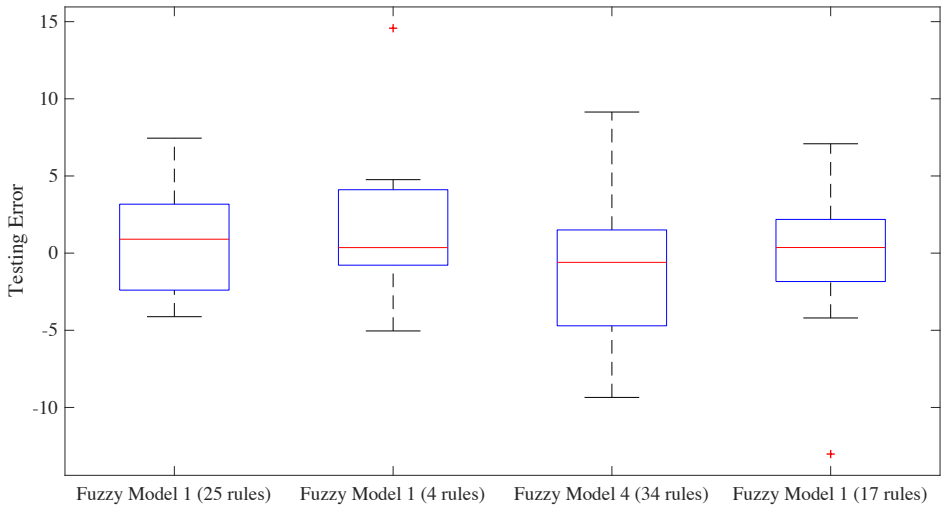


Figure 3.8 Testing error variability for the Fuzzy Models with smallest mean absolute testing error: Fuzzy Model 1 (25 rules – grid partition), Fuzzy Model 1 (4 rules – subtractive clustering), Fuzzy Model 4 (34 rules – subtractive clustering) and Fuzzy Model 1 (17 rules – subtractive clustering).

The means of the testing errors of Fuzzy Model 1 (25 rules), Fuzzy Model 1 (4 rules), Fuzzy Model 4 (34 rules), and Fuzzy Model 1 (17 rules) are not statistically different from zero (t-test p=0.298, p=0.252, p=0.447, p=0.795, respectively). The error distribution for Fuzzy Model 4 is wider, showing a more significant variability between patients. Fuzzy Model 1 (17 rules) is clearly centered on zero, with an IQ range [-3.32 2.60] ml.

Figure 3.9 shows the results of the Fuzzy Model 1 with 25 rules (grid partition), 4 rules (subtractive clustering) and 17 rules (subtractive clustering) on the training (Figure 3.9a)) and testing (Figure 3.9b)) data sets. The test errors of Fuzzy Model 1 with 25 rules and Fuzzy Model 1 with 4 rules are not statistically different (t-test p=0.918); however, there is a clear difference between training errors.

The output surface for the Fuzzy Model 1 with 25 rules is presented in Figure 3.10. Higher drops in SAP and BIS are associated with higher amounts of the drug as expected. However, it seems that overall, the model response is more influenced by SAP.

Conclusions and Future Work

A. Conclusions

The objective of this preliminary study was achieved, showing that fuzzy systems can be used in modelling of biomedical systems capturing relevant information.

The correlation analysis showed that patient's age, patient's LBM, the percentage of heart rate at LOC in relation to the baseline and the percentage of EMG at LOC in relation to the baseline are not statistically related to the total infused volume of propofol until LOC. As propofol is infused into the patient, both systolic blood pressure and BIS tend to decrease.

Regarding the TSK models, the best performance was achieved with Fuzzy Model 1 with 25 rules using grid partition and 17 rules using subtractive clustering. They both presented a small testing error and a right balance between training and testing data sets. Fuzzy Model 1 with 17 rules had the smallest testing error variability and had a more significant testing error average of zero (*t-test*, p=0.795) and the best balance between training and testing data sets. This fuzzy model used as inputs a variable related to the cerebral effect of propofol (BIS) and a variable related to the hemodynamic effect (SAP), had acceptable prediction properties and was able to capture the information in the data. On the other hand, the patient's age and LBM seem to worsen the performance of the prediction. When these variables were added to the model, its performance was worse. The same happened when only the hemodynamic variables (HR and SAP) were used or when only the brain monitor variables (BIS and EMG) were used. It seems that the combination of the information between BIS and SAP is essential in the prediction of the total amount of propofol until LOC.

Studies with interesting results use measures such as the twitch response to electrical stimulus to predict LOC. However, these are not standard monitors approved or used for clinical practice, and they are not yet related to the amount of drugs required to achieve LOC.

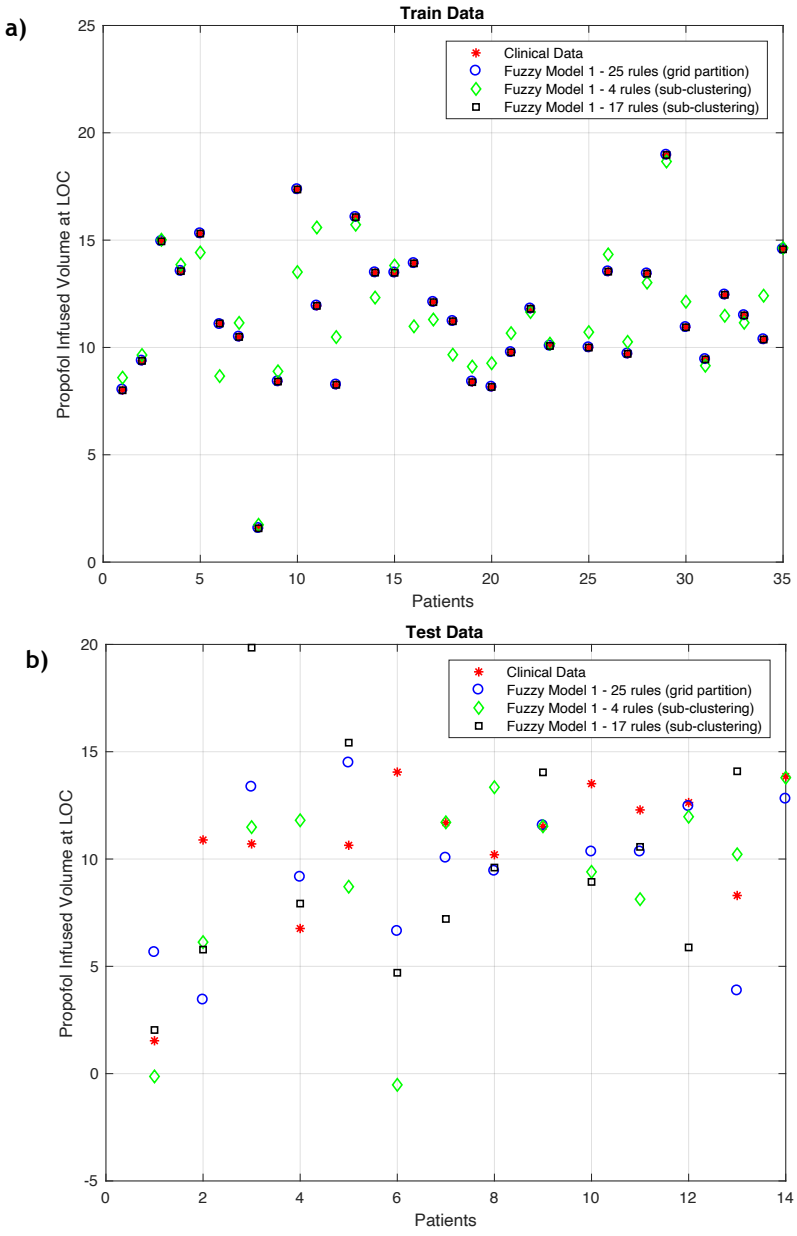


Figure 3.9 Results of the Fuzzy Model 1 with 25 rules (grid partition), with 4 rules (subtractive clustering) and with 17 rules (subtractive clustering): a) on the training data; b) on the testing data.

B. Future Works

The possibility of predicting the total amount of propofol required for LOC during general anesthesia will allow individualization of patients' needs. Furthermore, safer and effective care will occur if anesthesiologists replace the recommendation of administering a specific amount of propofol (based on a patient's weight and age) with monitoring the patient's response (BIS and SAP) to precisely identify the moment loss of consciousness occurs, identifying the amount of propofol each patient requires. This information could further be used to individualize the infusion rate of propofol required to maintain an adequate anesthesia level during the surgery.

In the future, it is intended to add more variables to the models, such as gender and another cerebral variable other than BIS. In addition, since in the anesthetic protocol of this study, only propofol was presented at LOC, and usually, an analgesic is also used, it is intended to collect more data with different anesthetic protocols and analyze the behavior of the fuzzy models when the interactions between the drugs are considered.

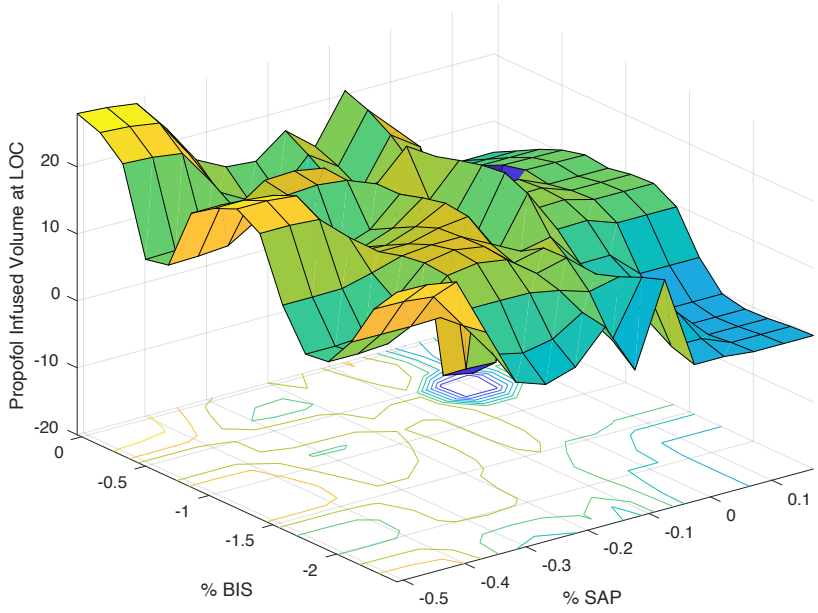


Figure 3.10 Output surface for the Fuzzy Model 1 using 25 rules.

4 PATTERNS OF HYSTERESIS BETWEEN INDUCTION AND EMERGENCE OF NEUROANESTHESIA

This chapter yields a better understanding of the transition from consciousness to unconsciousness and vice-versa. Recovery consciousness has classically been seen as a mirror process of loss of consciousness. However, animal findings initially suggested that this process was different, presenting a hysteresis pattern between drug concentration at loss and recovery of consciousness. This may contribute to anesthesia's personalization during the maintenance phase, as the concentration of hypnotic necessary to induce unconsciousness is not necessarily the same to recover consciousness.

This study led to a published paper in the Journal of Neurosurgical Anesthesiology, in 2020:

i. Patterns of Hysteresis Between Induction and Emergence of Neuroanesthesia are Present in Spinal and Intracranial Surgeries.

It also led to one abstract presented at the American Society of Anesthesiologists Annual Meeting 2016 and one abstract presented at the SNACC's 44th Annual Meeting:

i. Evidence of neural inertia in humans.
ii. Hysteresis at loss and return of consciousness with propofol anesthesia in surgical patients may be evidence of neural inertia in humans.

Patterns of hysteresis between induction and emergence of neuroanesthesia are present in spinal and intracranial surgeries

Ana Leitão Ferreira MS, Rui Correia MS, Sérgio Vide MD, Ana Dias Ferreira MD, Max B Kelz MD, PhD, Joaquim Gabriel Mendes PhD, Catarina S Nunes PhD, Pedro Amorim MD

Abstract

Background: Recovery of consciousness is usually seen as a passive process, with emergence from anesthesia depicted as the inverse process of induction resulting from the elimination of anesthetic drugs from their central nervous system sites of action. However, that need not be the case. Recently it has been argued that hysteresis might be encounter changes in the state of consciousness, known as neural inertia. This phenomenon has been debated in neuroanesthesia, as manipulation of the brain might further influence recovery of consciousness. The present study is aimed at assessing hysteresis between induction and emergence under propofol-opioid neuroanesthesia in humans using estimated propofol concentrations in both spinal and intracranial surgeries.

Methods: It was identified the moments of loss (LOR) and recovery of responsiveness (ROR) in 21 craniotomies and 25 spinal surgeries. Propofol was given slowly until loss of responsiveness and stopped at the end of surgery. An opioid was present at induction and recovery. Propofol infused was recorded and plasma and effect-site concentrations were estimated using two pharmacokinetic models. Dose-response curves were generated. Estimated propofol plasma and effect-site concentrations were compared to assess hysteresis.

Results: Estimated propofol concentrations at LOR and ROR showed hysteresis. Whether for spinal or intracranial surgeries, the EC_{50} of propofol at which half of the patients entered and exited the state of responsiveness was significantly different.

Conclusions: Hysteresis was observed between propofol concentrations at LOR and ROR, in both groups of patients presenting for spinal and intracranial surgeries. Manipulation of the brain does not appear to change patterns of hysteresis, suggesting that neural inertia may occur in humans, in a way similar to that found in animal species. These findings justify performing a clinical study in patients using measured propofol concentrations to assess neural inertia.

Introduction

Recovery of consciousness and responsiveness (ROR) has been viewed for many years as the inverse process of anesthetic induced loss of responsiveness (LOR) [12]. However, accumulating evidence suggests that this might not be the case. Consequently, debate whether the asymmetry between the anesthetic concentrations required for induction and emergence (anesthetic hysteresis) is due to pharmacokinetic characteristics or intrinsic neural mechanisms persists [110]. Increased understanding of the mechanisms enabling anesthetic emergence, could eventually convert today's passive clinical approach into a pharmacological intervention to actively modulate arousal [12], [111].

The hysteretic dissociation of anesthetic induction from emergence was first described in mice and fruit flies [110], [112], with lower concentrations of anesthetics required for emergence. This hysteresis could not be explained solely by pharmacokinetics and the existence of a barrier termed ''neural inertia'' was proposed. The neural inertial barrier promotes maintenance of wakefulness or anesthesia and presumably exists to oppose rapid and potentially catastrophic transitions between these states.

Evidence supporting or refuting hysteresis with general anesthesia in humans has since been investigated. Three recent studies [66][113][114] have sought to clarify this by measuring dose-response curves for emergence and induction of general anesthesia. However, evidence remains to be conclusive, with neural inertia being observed in humans only under some circumstances. Kuizenga and colleagues [66] found evidence supporting neural inertia with some sevoflurane-based regimens but intriguingly, not with propofol. In the Warnaby study [113] with volunteers who received only propofol, showing evidence supporting neural inertia using predicted propofol concentrations at loss and return of conscious also failed. Nevertheless, Warnaby and colleagues [113] demonstrate that EEG slow wave activity saturation was asymmetric during induction and emergence. They suggest that slow wave activity saturation might be a signature of neural inertia in humans. In the study by Sepúlveda and colleagues [114], hysteresis between loss and recovery of responsiveness in volunteers with propofol was observed, although they stated their results cannot definitively confirm the presence of neural inertia. Some of these studies suggest that hysteresis is not likely due to pharmacokinetic mechanisms alone but might be explained by different pathways and neural circuits that drive the hypnotic effects of each drug. However, study designs could influence the detection of neural inertia and lead to false positive results [115].

The asymmetry between LOR and ROR has also been discussed in neuroanesthesia but regarding the influence of surgical manipulation of the brain during intracranial procedures and if changes in intracranial

pressure might influence hysteresis. To clarify this, it was conducted a clinical study in patients presenting for intracranial and spinal surgeries under propofol and opioid anesthesia. Under a well-defined clinical protocol, estimated propofol plasma (Cp) and effect-site (Ce) concentrations were determined to assess hysteresis at the moment of LOR and ROR by applying both the Schnider's and the Marsh's pharmacokinetic (PK) models. Neurosurgical patients requiring both craniotomies for excision of brain tumors and spinal surgeries were specifically included to evaluate if the estimated concentrations at LOR and ROR would differ between intracranial and spinal procedures.

Methods

A. Anesthetic protocol

Under institutional review board approval and written informed consent, consecutive adult patients undergoing routine neurosurgical procedures, expected to last for more than 90 minutes, were anesthetized as described below. Craniotomies were performed both for supra and infratentorial tumors. Spinal surgeries included laminectomies, decompressions, and fusions. Dates of enrollment were from March 2016 to July 2016.

Exclusion criteria were any alterations in mental status or bispectral index (BIS) < 90 before induction, significant cardiovascular, renal, hepatic or respiratory pathology and obesity (BMI>35kg/m^2). Procedures done by the same anesthesiologist over a five-month period were included.

None of the patients was pre-medicated. In the operating room, after placement of standard monitors and placement of an intravenous line in the dorsum of the hand, an infusion of an equilibrated electrolytic solution was started at 6mL/kg/h. Clinical practice for neurosurgical procedures consists of opioid-propofol anesthesia using a Target Controlled Infusion (TCI) system. Anesthesia began with a fentanyl bolus of 3µg per kg of ideal body weight (IBW). Four minutes later, a tourniquet was applied to the arm 20 cm above the venous catheter and a bolus of 20 mg of lidocaine was administered to reduce the pain associated with propofol and the limb withdrawal responses associated with rocuronium [116][117]. Propofol was administered using a Fresenius Base Primea docking station (Fresenius-Kabi, Bad Homburg, Germany) with two Fresenius Module DPS pumps. Intravenous infusion of 1% propofol started at 3.3 mL/kg/h. This slow velocity of infusion during induction enables a careful titration of the minimum amount of propofol required for LOR and allows for precise documentation of the moment of loss of consciousness. By using a TCI enabled device, estimated drug concentrations are constantly processed and displayed with 1-second

iterations. Once propofol reached the venous catheter, the tourniquet was released. The level of consciousness was assessed every 10 seconds using the Modified Observer's Assessment of Anesthesia and Sedation (OAA/S) scale [36]. At this point, no additional analgesic/opioid medication was given during induction. At LOR, defined as an OAA/S score of zero (lack of response to name calling and compression of the trapezius on the shoulder) the propofol infusion was stopped. The amount of propofol given (in mg) and the Ce and Cp were noted and the Fresenius Base Primea system was switched to effect-site TCI mode, with a target Ce lower than the Ce at LOR through the application of a previously presented formula [80]. Manual ventilation was started, a neuromuscular block monitor (Train-of-Four - TOF) was calibrated and rocuronium was then administered at 0.6 mg/kg. When no responses from TOF were present (TOF equal to 0), laryngoscopy and intubation were performed. After intubation, propofol was titrated to maintain Bispectral Index (BIS) between 40 and 60. Remifentanil by TCI was started 30 minutes after LOR and titrated during surgery. Propofol, fentanyl and remifentanil Ce were calculated using Schnider's [14], Shafer's [118] and Mintos´s [78] pharmacokinetic (PK) models, respectively. At the end of surgery, remifentanil Ce was fixed at 2.0 ng/mL and propofol infusion was stopped. The patient was called in a loud voice every 10 seconds and told to open his/her eyes. The moment of eye-opening was considered the moment of ROR. At that exact moment, the propofol Ce and Cp and the total amount of propofol given were recorded. The infused volumes data was used to estimate Ce and Cp with Marsh's PK model. Data recording was performed using Rugloop® software (Demed, Genk, Belgium), installed on a dedicated computer. This software communicates with Datex/GE monitor, BIS monitor and Fresenius Base Primea system. Rugloop software collects data every 5 seconds. Data collection ended ten minutes following extubation.

B. Statistical Methods

To determine the primary endpoint and evaluate for potential hysteresis between induction and emergence in patients presenting for neuroanesthesia, we relied on the study of Nunes et al. [119] that showed an average paired difference between the estimated Ce concentrations of propofol at LOR and ROR of 3.73 ± 0.92 μg/mL. Importantly, however, opioids were not present at LOR in the Nunes study [119]. In the present study, since an opioid was present at induction, it was expected that the propofol concentration required for LOR would be smaller and, therefore the expected difference between concentrations of propofol at LOR and ROR would also be smaller. Sample size calculation was performed to detect a

difference of 1 μg/mL, with 95% power, $\alpha = 1\%$ and the same 0.92 standard deviation of the paired response difference [119] (Sample size paired t-test, StatsDirect V3). A minimum sample size of 19 pairs/patients was obtained. Considering the two types of procedures performed in neurosurgery (craniotomies and spinal surgeries) and considering a 20% exclusion rate, a final samples size of 46 patients was established.

Propofol estimated concentrations at LOR and at ROR were analyzed and compared in all the patients, and in each of the two subgroups of surgical procedures: craniotomies and spinal surgeries. Following the assessment of the primary hypothesis, the second step was to determine the dose-response curves.

To generate the dose-response curves for LOR and ROR, propofol Ce data at LOR were sorted from the lowest to the highest value in order to obtain the percentage of awake patients for each specific concentration. Constraints were used when determining all dose-response curves such that at the highest propofol Ce all patients were assumed unconscious and in the absence of propofol, all patients were assumed to be conscious. Both of these assumptions prove experimentally valid. Dose-responses curves for LOR and ROR were then generated for the entire group of patients and for the two subgroups. To adjust the response curves to the data, sigmoidal dose-response and variable slope function as described elsewhere [110][120] were used. This non-linear regression model parameters were: the bottom and top plateaus of the curve, representing the minimum and maximum values of the percentage of awake patients; the EC_{50}, representing the concentration of that drug at which 50% of the effect was observed, and the Hill's slope representing the steepness of the curve. This curve was symmetrical around its inflection point, which was defined as the point on the curve where the curvature changes direction. The bottom was set to 0 and top to 100. No constraints were placed on the Hill's slope or EC_{50} fit parameters.

The third step was to calculate the area between the LOR and ROR sigmoidal dose-response curves. For that, both LOR and ROR sigmoidal dose-response curves were mathematically integrated over the range of the LOR curve EC_1 (the concentration at which 1% of the patients had not yet entered into anesthetic state) to the ROR curve EC_{99} (the concentration at which 99% of the patients had exited the anesthetic state), as detailed elsewhere [110]. This integration yielded an area (difference between the integrated LOR sigmoidal dose-response curve and the integrated ROR curve) that is a unit-less quantitative measure of the resistance to transitions between arousal states, which is, by definition, neural inertia.

All previous steps were repeated using propofol concentrations as estimated by the Marsh's PK model.

Propofol Cp and Ce values for the Marsh's PK model were estimated using the infused propofol volumes recorded at 5 seconds intervals during each case.

Paired variables were compared with the Student's t-test or the Wilcoxon's matched pairs test as appropriate for the data distribution. Correlation analyses were performed using the Spearman's or the Pearson's method as appropriate for the data distribution. Comparisons between data from patients presenting for intracranial and spinal surgeries were performed with the Students' t-test for independent samples or Mann-Whitney, depending on the data distribution. Comparison of neural inertia obtained between models was performed with one-way ANOVA.

A *p*-value lower than 0.01 was considered statistically significant.

Results are presented as mean ± standard deviation (SD) or mean [95% CI: lower limit, upper limit] for the normally distributed variables and as median (P_{25}-P_{75}) for the non-normally distributed variables (explicitly mentioned).

Statistical analysis was performed using MATLAB® 2014a (MathWorks, Inc., Natick, MA) and IBM SPSS Statistics® (IBM Corporation, NY).

Results

A total of 46 neurosurgical patients were included in this study, 25 presenting for spinal surgery and 21 presenting for intracranial surgery. One patient presenting for intracranial surgery was excluded from the analysis due to an error in data recording, therefore, data from 45 patients are presented. Demographics for all 45 patients were: 58±13 years of age, 68±12 kg, 164±8 cm, 25±4 BMI, 20 males and 25 females, 4 ASAI, 31 ASAII and 10 ASAIII. Demographics for the 20 patients presenting for craniotomies were: 55±16 years of age, 67±11 kg, 166±8 cm, 24±4 BMI, 9 males and 11 females, 1 ASAI, 13 ASAII and 6 ASAIII. Demographics for the 25 patients presenting for spinal surgeries were: 60±10 years of age, 69±13 kg, 163±7 cm, 26±4 BMI, 12 males and 13 females, 3 ASAI, 18 ASAII and 4 ASAIII. There were no statistically significant differences in demographic data between patients presenting for craniotomies and spinal surgeries (Table 4.1).

Estimated propofol, fentanyl and remifentanil plasma and effect-site concentrations at LOR and ROR for all surgeries and for the sub-groups of craniotomies and spinal surgeries are presented in Table 4.2, results expressed with regard to the 95% Confidence Intervals (CI) for the sample mean. For the moment of LOR and considering all surgeries, estimated effect-site drug concentrations were: fentanyl 3.48 [3.38;3.58] ng/mL, propofol 4.04 [3.58;4.50] µg/mL using the Schnider's PK model and 2.92 [2.58;3.25] µg/mL using the Marsh's PK model. For the moment of ROR, estimated effect-site concentrations were:

for fentanyl 0.30 [0.29;0.32] ng/mL, for remifentanil 2.06 [1.99;2.13] ng/mL, and for propofol 1.09 [0.98;1.20] μg/mL using the Schnider's PK model and 1.34 [1.21;1.48] μg/mL using the Marsh's PK model. Estimated plasma concentrations for the same drugs, at the same moments and using the same PK models are presented in Table 4.2.

Table 4.1 Demographic Data From All 45 Patients Divided According to the Type of Surgery. Results are Mean ± Standard Deviation. There Were No Statistically Significant Differences Between the Two Groups (p>0.001).

	Craniotomies (n=20)	Spinal surgeries (n=25)	p-value[a]
Age (years)	55 ± 16	60 ± 10	0.114
Weight (kg)	67 ± 11	69 ± 13	0.530
Height (cm)	166 ± 8	163 ± 7	0.197
BMI	24 ± 4	26 ± 4	0.154
Gender	9 Males / 11 Females	12 Males / 13 Females	0.304
ASA	1 ASAI / 13 ASAII / 6 ASAIII	3 ASAI / 18 ASAII / 4 ASAIII	0.155

[a] p-value is based on Chi-Square test for the categorical variables, and is based on 2-sample t-test for the continuous variables.

Opioid and propofol estimated concentrations in patients presenting for craniotomies and patients presenting for spinal surgeries are discriminated in Table 4.2 as well. Estimated propofol concentrations for all patients at LOR were, on average, 2.94 [2.52; 3.36] μg/mL higher than the concentrations at ROR, using the Schnider's PK model. Propofol estimated concentrations at LOR were always significantly higher than estimated concentrations at ROR, both for plasma and effect-site concentrations, using either the Schnider's or the Marsh's PK models and for comparisons within each of the two subgroups of patients (Table 4.2).

Table 4.2 Propofol, Fentanyl, and Remifentanil Estimated Concentrations at LOR and ROR in All 45 Patients, in the Patients Subjected to Craniotomies Only and in Patients Submitted to Spinal Surgeries.

	All surgeries		Intracranial surgeries		Spinal surgeries	
	LOR (n=45)	ROR (n=45)	LOR (n=20)	ROR (n=20)	LOR (n=25)	ROR (n=25)
Ce propofol (Schnider) (µg/mL)	4.04 [3.58;4.50]	1.09 [0.98;1.20]	3.93 [3.25;4.62]	1.11 [0.93;1.28]	4.12 [3.46;4.79]	1.08 [0.93;1.23]
	2.94 [2.52; 3.36] p<0.001		2.82 [2.18; 3.47] p<0.001		3.04 [2.45; 3.64] p<0.001	
Cp propofol (Schnider) (µg/mL)	8.40 [7.94;8.86]	0.88 [0.79;0.97]	8.09 [7.32;8.86]	0.96 [0.80;1.11]	8.65 [8.07;9.22]	0.82 [0.70;0.93]
	7.52 [7.08; 7.97] p<0.001		7.14 [6.38; 7.90] p<0.001		7.83 [7.29; 8.37] p<0.001	
Ce propofol (Marsh) (µg/mL)	2.92 [2.58;3.25]	1.34 [1.21;1.48]	2.92 [2.40;3.44]	1.39 [1.15;1.64]	2.91 [2.44;3.38]	1.30 [1.14;1.46]
	1.57 [1.26; 1.89] p<0.001		1.52 [1.06; 1.99] p<0.001		1.61 [1.16; 2.06] p<0.001	
Cp propofol (Marsh) (µg/mL)	4.09 [3.78;4.39]	1.27 [1.15;1.39]	4.08 [3.60;4.56]	1.33 [1.10;1.56]	4.09 [3.67;4.51]	1.22 [1.08;1.36]
	2.81 [2.54; 3.09] p<0.001		2.75 [2.32; 3.17] p<0.001		2.87 [2.47; 3.26] p<0.001	
Ce fentanyl (Shafer) (ng/mL)	3.48 [3.38;3.58]	0.30 [0.29; 0.32]	3.55 [3.38;3.72]	0.28 [0.25;0.32]	3.44 [3.31;3.56]	0.32 [0.30;0.34]
Cp fentanyl (Shafer) (ng/mL)	2.11 [2.04;2.18]	0.30 [0.28; 0.32]	2.16 [2.03;2.29]	0.28 [0.24;0.31]	2.07 [1.99;2.15]	0.31 [0.30;0.33]
Ce remifentanil (Minto) (ng/mL)	-	2.06 [1.99;2.13]	-	2.01 [2.00;2.02]	-	2.11 [1.96;2.14]
Cp remifentanil (Minto) (ng/mL)	-	2.03 [1.98;2.08]	-	2.01 [2.00;2.02]	-	2.05 [1.96;2.14]

The average time from the moment propofol infusion was started until LOR (2.29±0.75 minutes) versus the estimated propofol Ce at LOR, the estimated propofol Ce concentrations at LOR versus at ROR for each patient and the average time from the moment propofol infusion was stopped until ROR (6.30±3.86 minutes) versus the estimated propofol Ce at ROR and versus the estimated propofol Ce when propofol infusion was stopped are shown in Figure 4.1.

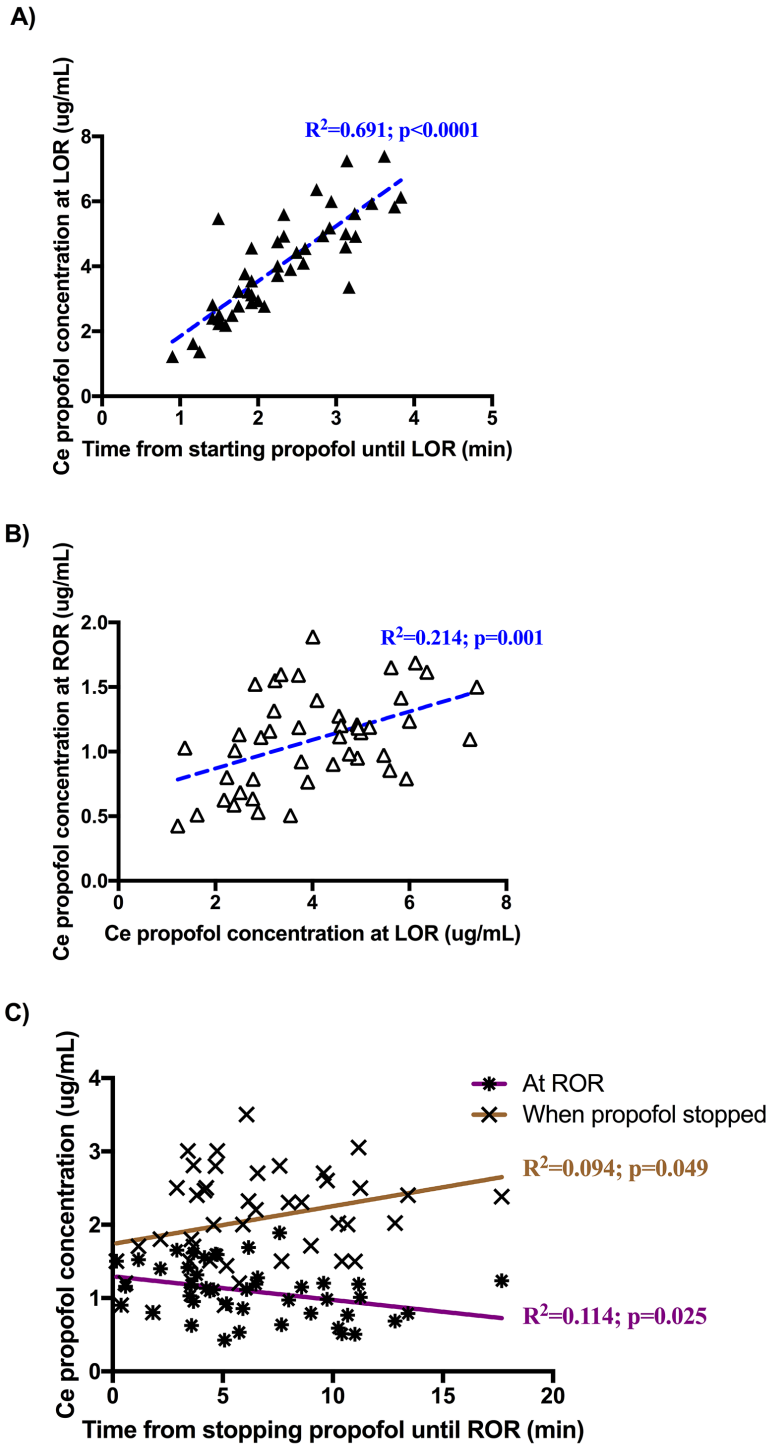


Figure 4.1 Relationship between individual estimated effect-site concentrations of propofol using Schnider's PK model for all patients: (A) Time (in minutes) from starting infusion of propofol until LOR versus estimated effect-site concentration (µg/mL) at LOR; (B) Estimated effect-site concnetration (µg/mL) at LOR versus estimated effect-site concentration (µg/mL) at ROC; (C) Time (in minutes) from stopping infusion of propofol until ROR versus estimated effect-site concentration (µg/mL) at ROR and estimated effect-site concentration (µg/mL) at the moment propofol infusion was stopped. Pearson's correlation test, p<0.01 represents a statistically significant correlation.

The average duration of anesthesia, considered as the time elapsed from LOR until stopping the propofol infusion was 3.40 [2.85; 3.94] hours, with anesthesia for craniotomies lasting significantly longer than for spinal procedures (p<0.001) (Table 4.3).

Table 4.3 Propofol and Remifentanil Estimated Effect-site Concentrations During Maintenance, Propofol Estimated Effect-site Concentration When Infusion was Stopped Before the End of the Procedure and Duration of the Procedure.

	All Surgeries (n=45)	Intracranial surgeries (n=20)	Spinal Surgeries (n=25)
Ce propofol (Schnider) during maintenance (µg/mL)	1.79 [1.48;2.09]	1.93 [1.35;2.51]	1.67 [1.33;2.01]
		0.26 [-0.36;0.88]; p=0.421	
Ce propofol (Schnider) when infusion is stopped (µg/mL)	2.06 [1.87;2.25]	2.06 [1.75;2.37]	2.06 [1.80;2.32]
		0.001 [-0.39;0.39]; p=0.994	
Ce remifentanil (Minto) during maintenance (ng/mL)	1.69 (1.35-2.72) †	2.55 (1.50-3.81) †	1.44 (1.30-1.89) †
		p=0.005	
Duration of the procedure (hours)	3.40 [2.85;3.94]	4.52 [3.49;5.56]	2.50 [2.30;2.70]
		2.02 [0.97;3.07]; p<0.001	

†Results are presented as median (P25-P75).

Propofol average estimated effect-site concentration for the maintenance phase of anesthesia was 1.79 [1.48; 2.09] µg/mL, for craniotomies it was 1.93 [1.35; 2.51] µg/mL and for spinal surgeries it was 1.67 [1.33; 2.01] µg/mL, not statistically different (p=0.421, Students' t-test for independent samples). At the moment propofol infusion was stopped following the end of surgeries, estimated propofol Ce for all patients was 2.06 [1.87; 2.25] µg/mL, for craniotomies it was 2.06 [1.75; 2.37] µg/mL and for spinal surgeries it was 2.06 [1.80; 2.32] µg/mL, not statistically different (p=0.994, Students' t-test for independent samples). Remifentanil estimated effect-site concentration during anesthesia maintenance for all patients was 1.69 (1.35-2.72) ng/mL, with the Ce for craniotomies being significantly higher than those for spinal surgeries (p=0.005, Mann-Whitney test). Mean arterial pressure at ROR was significantly higher than at LOR, but heart rate at LOR and ROR and end-tidal CO_2 at LOR (second breath after tracheal intubation) and ROR were similar (Table 4.4). Arterial pressure, heart rate and end-tidal CO_2 at both LOR and ROR did not differ between patients presenting for craniotomies and spinal surgeries. Intra-operative blood loss did not mandate a blood transfusion in any patient. The goodness-of-fit measures for the LOR and ROR sigmoidal dose-response curves were the adjusted R-squared (coefficient of determination) which ranged from 0.97 to 0.99 and the root mean squared error which ranged from 2.60 to 5.10 with a median value of 3.93.

Table 4.4 End-tidal of CO2, Heart Rate and Mean Arterial Pressure at LOR and ROR for All, Spinal and Intracranial Surgeries. Comparisons Were Made Between the Values at LOR and ROR (Paired Student's T-Test or Wilcoxon as Appropriate). P<0.001 Represents a Statistic Significant difference.

	All surgeries		Intracranial surgeries		Spinal surgeries	
	LOR (n=45)	**ROR (n=45)**	**LOR (n=20)**	**ROR (n=20)**	**LOR (n=25)**	**ROR (n=25)**
End-tidal CO_2 (%)	5.16 [4.90;5.42]	5.12 [4.90;5.35]	5.40 (4.57-5.85) †	4.90 (4.6-5.4) †	5.10 [4.80;5.40]	5.28 [5.02;5.55]
	0.03 [-0.30;0.37]; p=0.838		0.50 [0.25;0.27]; p=0.251		-1.18 [-0.51;0.14]; p=0.254	
Heart rate (beats/min)	67.59 [63.51;71.67]	67.86 [62.72;73.00]	65 (64-69.5) †	66 (60-81) †	62 (59-71) †	67 (67-78) †
	-0.27 [-6.29;5.75]; p=0.928		-1.00 [0.47;0.49]; p=0.943		4.00 [0.53;0.54]; p=0.529	
Mean arterial pressure (mmHg)	96.40 [91.17;101.62]	78.81 [74.86;82.76]	95.49 [87.26;103.71]	76.82 [71.64;81.99]	97.09 [89.83;104.35]	80.33 [74.34;86.32]
	17.58 [11.65;23.52]; p<0.001		18.67 [9.30;28.05]; p=0.001		16.76 [8.54;24.98]; p<0.001	

†Results are presented as median (P25-P75).

These values showed an overall very good fit to the data. In Table 4.5 are displayed the EC_{50} and the Hill's slope parameters obtained from the fitting of the non-linear regression models. All values are reported along with their corresponding 95% CI. Propofol concentrations at which half of the patients entered and exited the state of responsiveness for induction were always statistically significantly greater than those at emergence ($p<0.001$), i.e. LOR (EC_{50}) > ROR (EC_{50}), for all patients, in the patients presenting for craniotomies and in the patients presenting for spinal surgeries (Table 4.5). These differences in the EC_{50} between LOR and ROR occurred using concentrations estimated using either the Schnider's and the Marsh's PK models (Table 4.5).

A more comprehensive description of the differences between propofol Ce concentrations (with the Schnider's PK model) at LOR and ROR is shown graphically by the shaded area between the dashed LOR and the solid ROR curves in Figure 4.2. The dose-response curves presented in Figure 4.2 considered the best-fit parameters of the non-linear regression model. Taking into account that both the Schnider's and the Marsh's PK models achieved sufficient bias and precision in prediction of target concentration [121][122][123], it was performed an extensive set of bootstrapping simulations using the published median performance errors by Glen and White [121], so as to establish the error margins for the estimated propofol Cp at LOR and ROR and observe whether hysteresis would still occur.

Table 4.5 Best-fit Parameters for LOR and ROR Sigmoidal Dose-response Curves Regarding All, Intracranial, and Spinal Surgeries.

		All surgeries		Intracranial surgeries		Spinal surgeries	
		LOR (n=45)	**ROR (n=45)**	**LOR (n=20)**	**ROR (n=20)**	**LOR (n=25)**	**ROR (n=25)**
Ce Schnider	**Hill's slope**	-3.87 [-4.08;-3.67]	-4.68 [-4.98;4.38]	-4.72 [-5.34;-4.10]	-5.81 [-6.59;-5.02]	-3.61 [-4.02;-3.20]	-4.17 [-4.61;-3.72]
	p-value	<0.001		0.040		0.078	
	EC_{50}	3.92 [3.87;3.97]	1.08 [1.07;1.10]	4.09 [3.99;4.20]	1.13 [1.11;1.16]	3.92 [3.79;4.05]	1.06 [1.04;1.09]
	p-value	<0.001		<0.001		<0.001	
Cp Schnider	**Hill's slope**	-10.41 [-11.04;-9.78]	-4.98 [-5.27;-4.68]	-9.19 [-10.6;-7.81]	-5.30 [-6.02;-4.58]	-11.1 [-12.43;-9.77]	-5.60 [-6.16;-5.04]
	p-value	<0.001		<0.001		<0.001	
	EC_{50}	8.31 [8.27;8.35]	0.86 [0.85;0.87]	8.19 [8.08;8.30]	0.97 [0.95;0.99]	8.47 [8.38;8.55]	0.80 [0.79;0.82]
	p-value	<0.001		<0.001		<0.001	
Ce Marsh	**Hill's slope**	-3.76 [-3.97;-3.55]	-4.85 [-5.10;-4.60]	-4.41 [-5.07;-3.75]	-5.09 [-5.54;-4.63]	-3.64 [-3.97;-3.30]	-4.81 [-5.31;-4.32]
	p-value	<0.001		0.108		<0.001	
	EC_{50}	2.82 [2.78;2.86]	1.30 [1.29;1.31]	3.01 [2.92;3.10]	1.37 [1.34;1.39]	2.77 [2.70;2.84]	1.28 [1.25;1.31]
	p-value	<0.001		<0.001		<0.001	
Cp Marsh	**Hill's slope**	-6.02 [-6.33;-5.71]	-5.07 [-5.35;-4.79]	-7.02 [-7.99;-6.04]	-5.11 [-5.50;-4.71]	-5.81 [-6.32;-5.30]	-5.15 [-5.69;-4.60]
	p-value	<0.001		0.001		0.088	
	EC_{50}	4.07 [4.04;4.10]	1.24 [1.22;1.25]	4.22 [4.15;4.29]	1.31 [1.29;1.32]	4.03 [3.97;4.09]	1.21 [1.18;1.23]
	p-value	<0.001		<0.001		<0.001	

In Figure 4.3 are presented the propofol dose-response curves considering 1000 simulations of the LOR and ROR concentrations for all patients, for the patients presenting for craniotomies and for the patients presenting for spinal surgeries. As it is observed in the graphs, hysteresis is still present, even when prediction errors of more than 50% are incorporated, which is the case at increasing concentrations for the Marsh's PK model [121].

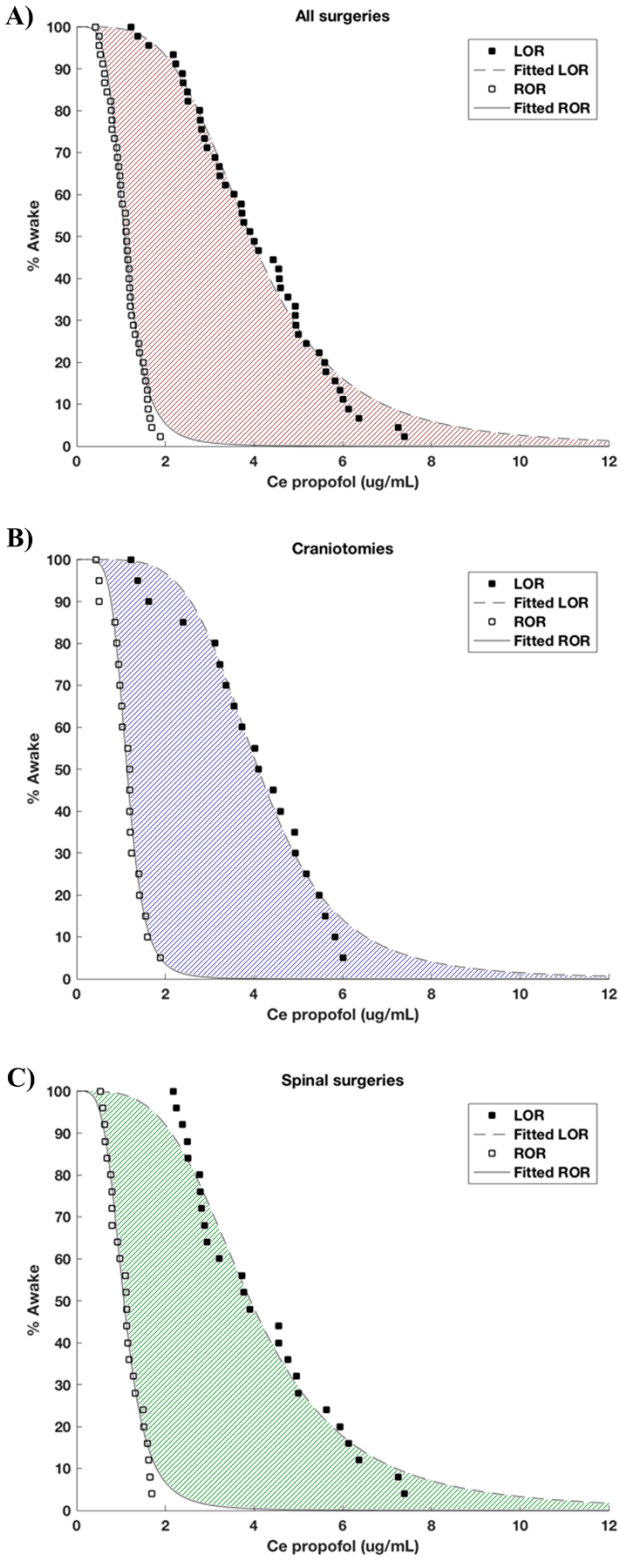


Figure 4.2 Hysteresis. Filled squares and their corresponding best-fit solid curve denote LOR. Open squares and their corresponding best-fit solid curve denote ROR. Within the shaded areas, patients will be awake or anesthetized depending upon their previous state of arousal. These areas represent a resistance to change in the state of consciousness. (A) Propofol dose-response curve in humans for LOR and ROR regarding all surgeries. (B) Propofol dose-response curve in humans for LOR and ROR regarding craniotomies only. (C) Propofol dose-response curve in humans for LOR and ROR regarding spinal surgeries only.

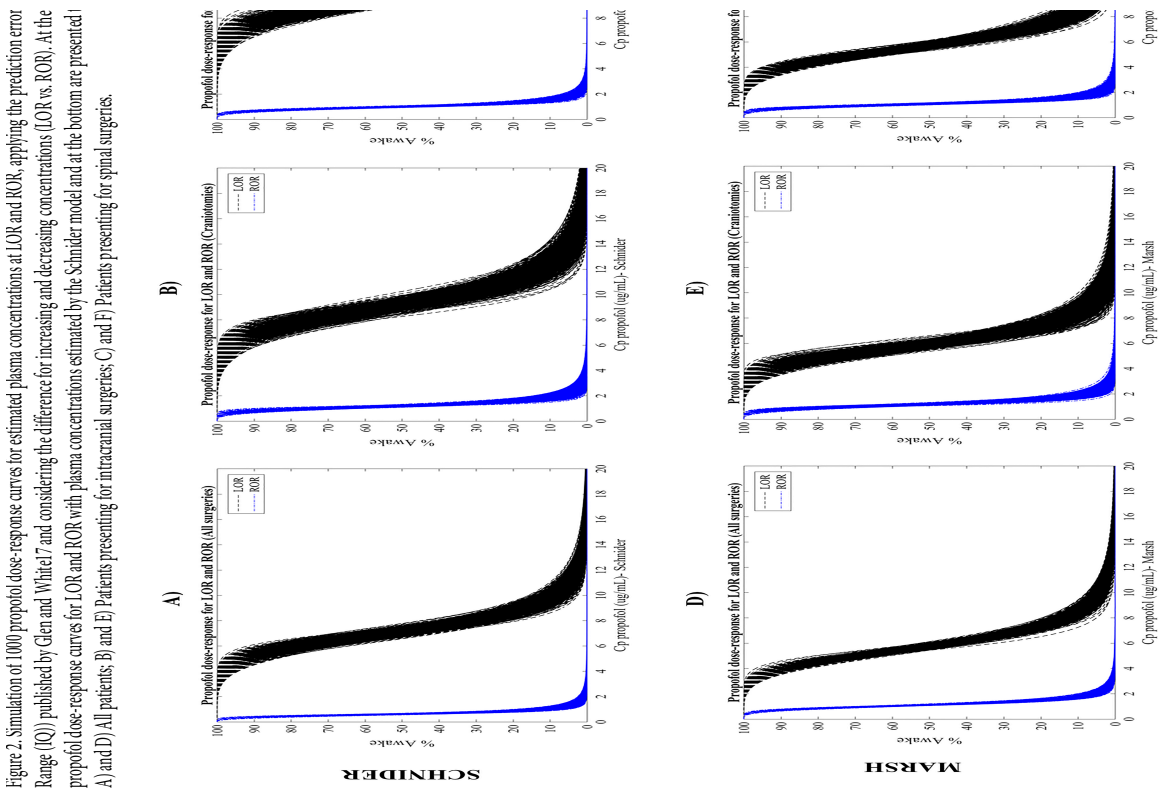


Figure 4.3 Simulation of 1000 propofol dose-response curves for estimated plasma concentrations at LOR and ROR, applying the prediction error margins (Interquartile Range (IQ)) published by Glen and White[121] **and considering the difference for increasing and decreasing concentrations (LOR vs. ROR). At the top are presented the propofol dose-response curves for LOR and ROR with plasma concentrations estimated by the Schnider model and at the bottom are presented those by the Marsh model. A) and D) All patients; B) and E) Patients presenting for intracranial surgeries; C) and F) Patients presenting for spinal surgeries.**

Discussion

The present study sought to determine whether a propofol-opioid anesthetic produces detectable neural inertia in a clinical setting and whether neural inertia might be affected by intracranial surgical procedures. It was determined that in these neurosurgical patients, presenting for procedures under total intra-venous anesthesia, it is possible to observe a pattern of anesthetic hysteresis consistent with neural inertia. Moreover, manipulation of the human brain in the presented clinical setting, did not change any of the findings as patients presenting for spinal procedures had indistinguishable anesthetic responses when compared with those needing intracranial resections.

Data showed that estimated propofol at EC_{50} for induction was greater than at EC_{50} for emergence, suggesting that emergence from anesthesia might not be the opposite mirror process of induction. However, this observation could be due to the use of effect-site target-controlled infusion systems to calculate the infusion regimen and estimating the effect-site concentration instead of measuring them [115].

Nevertheless, the Hill slopes in this study indicate the same variability between the anesthetic concentrations at induction and emergence in both intracranial and spinal surgeries.

The design of this study was unfortunately suboptimal to address the question of whether the hysteresis is due to pharmacokinetic mechanisms or intrinsic neural mechanisms. First, these results are partially confounded because at induction, patients received fentanyl before the propofol infusion and then remifentanil for the maintenance phase and until emergence. Despite the fact that, from the point of view of its kinetic-dynamic dissociation, a bolus of fentanyl could not be comparable with TCI remifentanil, from the point of view of its kinetic-dynamic dissociation, theoretically, it would be in Cp equipotent according to the literature reference [124][125]. We modeled the fentanyl concentrations at the moments of LOR and ROR, considering the relationship in potency among opioids, and, opioid concentrations at those moments can be considered clinically equipotent. Also, the measurements used to calculate hysteresis were based on estimated and not measured propofol concentration. We performed estimations with the Marsh's and the Schnider's PK models and for both plasma and effect-site estimates. Having measured real plasma concentrations at both LOR and ROR would have provided stronger evidence in favor or against hysteresis. However, analysis of the results applies caution and is performed addressing the limitations of using modeled concentrations. Such limitations may be due to the known errors that have been identified when comparing estimated with real concentrations [121], with the knowledge that such errors tend to increase during the dynamic phases of anesthesia (induction and recovery) and with the known differences in pharmacokinetic models when estimating propofol concentrations. To check these, it was performed an extensive set of simulations considering the prediction errors for the estimated plasma concentrations at LOR and ROR. In results, patterns of hysteresis are still present even when prediction errors of more than 50% are incorporated. Finally, results focus on the estimated propofol concentrations at LOR and ROR, but these moments depend not only on the effect of propofol but also on the opioids' effects, given the known synergism between both drugs. Despite this, this study offers the advantage of addressing the real scenario of clinical anesthesia with concomitant surgical intervention. Other factors that could impact on the transitions between responsiveness and unresponsiveness are related to physiologic variables that impact on anesthetic delivery to the brain, namely cardiac output and cerebral blood flow. Although none of these variables was measured directly, end-tidal CO_2, which could alter cerebral blood flow, did not differ between LOR and ROR, while heart rate and blood pressure, that can be related to cardiac output, showed heart rate to be the same at LOR and ROR but mean arterial pressure to be significantly lower at ROR,

implying that at ROR cardiac output could be lower. While cardiac output clearly influences the way anesthetics reach the brain, the implication of cardiac output on the brain dynamics of propofol exiting the brain, if indeed that phenomenon happens, remains to be understood.

Despite the concerns previously described and in support of these findings, hysteresis was present in a similar way in both craniotomies and spinal surgeries. Statistically, the only differences between patients having spinal and intracranial surgeries in the results were in anesthesia duration and in the amount of remifentanil required during maintenance. Such differences are not expected to interfere with the main findings.

There were some differences in the current study when compared with other studies that assessed neural inertia [110][114][66], namely at ROR, in which patients were under significant nociceptive stimulation. At ROR, patients still had a tracheal tube in place and had just finished a surgical procedure that left them with a surgical wound. This incision was not present at LOR when no nociceptive stimulation was present. These stimuli present at the end of surgery could contribute to some arousal and consequently to higher concentrations of propofol at ROC. Although these studies are aimed to assess the existence of neural inertia in humans, data pertains to patients undergoing longer anesthetics for surgical procedures. Duration of anesthesia might also have some influence in the presence of hysteresis.

Results show that independently of neural inertia existing in humans, intracranial procedures do not change hysteresis. Nevertheless, better understanding the switching between consciousness and unconsciousness is of uttermost importance. Acknowledging the existence of a wide inter-patient variability in drug requirements for LOR as well as the existence of hysteresis between drug concentrations at LOR and ROR, could result in an important step towards the implementation of personalized medicine to anesthesiology.

Therefore, the next step should be a study in humans, presenting for surgery under general anesthesia performed with propofol and maintain the same concentration of opioid at LOR and ROR, with plasma propofol and opioid measurements performed at several stages and very precise identification of the moments of LOR and ROR.

5 ELECTROENCEPHALOGRAPHY IN THE DETECTION OF LOSS OF CONSCIOUSNESS

This chapter is divided into two main sections, section 5.1 presenting a study developed to examine electroencephalogram signatures that could be associated with the time of loss of consciousness; section 5.2 presents a study developed to improve the detection of the transition to unconsciousness by applying machine learning techniques to the raw frontal electroencephalogram.

The study described in the first section led to a published paper:

i. EEG signatures at the transition between conscious and unconscious state during induction of general anesthesia with remifentanil and propofol; Proceedings of the IEEE International Symposium on Medical Measurements and Applications (MEMEA), 2018; 587-591.

The study presented in the second section resulted in one paper accepted for publication in IRBM Innovation and Research in BioMedical engineering:

i. Implementation of neural networks to frontal electroencephalography for the identification of the transition responsiveness/unresponsiveness during induction of general anesthesia.

This chapter is organized as follows:

5.1 EEG signatures at the transition between conscious and unconscious.

5.2 Implementation of neural networks to frontal electroencephalography for the identification of the transition responsiveness/unresponsiveness during induction of general anesthesia.

5.1 EEG signatures at the transition between conscious and unconscious

Ana Leitão Ferreira MSc, Joaquim Gabriel Mendes PhD, Pedro Amorim MD, Catarina Nunes PhD

Abstract

Precisely identifying the moment of Loss of Consciousness (LOC) during the induction phase of general anesthesia is of extreme importance for individualizing the patient's needs. In the lack of an objective method to assess this moment, a new methodology is needed. In this observational study, it was examined Electroencephalogram (EEG) signatures associated with the moment of LOC as a starting point to create a robust and well-supported model for tracking the dynamic changes between conscious and unconscious states. It was used data from 12 patients under general anesthesia for neurosurgical procedures with remifentanil and propofol. Multitaper spectrograms were computed to observe the dynamics of EEG oscillations before and after LOC. At LOC, it was identified a decrease in gamma power and an increase in delta and alpha bands.

Keywords: remifentanil; propofol; electroencephalogram; spectrogram; loss of consciousness.

Introduction

General anesthesia is a drug-induced, reversible condition that produces unconsciousness, analgesia, amnesia, and akinesia with maintenance of physiological stability [26]. Different anesthetic drugs are commonly used to achieve these, such as hypnotics, analgesics, and muscle relaxants. Of the behavioral states, unconsciousness is perhaps the most fascinating, and it is in this thesis the focus since the muscle relaxant drug has no proven influence on the degree of unconsciousness. The analgesic drug is of great importance since it affects the anesthetic drug's pharmacodynamics, interacting with each other to achieve adequate levels of depth of anesthesia and analgesia [126].

Monitoring depth of anesthesia is an elusive goal because of the poorly definition of depth of anesthesia. Most available monitors claim to reflect the hypnotic component of anesthesia, but analysis of the level of consciousness still lacks precision. The Electroencephalogram (EEG), which measures the brain's spontaneous electrical activity using non-invasive electrodes attached to several locations of the patient's head [37], has long been considered the most feasible approach for tracking brain states under general anesthesia. However, reading the EEG has not become part of routine anesthesiologists' practice. Instead, the depth of anesthesia monitors compute proprietary indices that reduce the EEG to a single number representing, indirectly, the patient's level of unconsciousness [127][128][129].

Identifying the precise moment of Loss Of Consciousness (LOC) during the induction phase of general anesthesia is extremely important because it will determine the hypnotic amount required for each patient and will provide important information to guide the infusion rate required to maintain adequate level of anesthesia, ensuring a safe and an effective care [107]. This will help to prevent intraoperative awareness episodes [130][131][132], and overdose [133].

In Purdon et al. [49], the authors analyzed the EEG oscillations' dynamics from volunteers subjected to anesthesia with propofol. They showed that, at LOC, both alpha (8-12Hz) and low-frequency (0.1-1Hz) power increases significantly. However, this was never done in patients under surgery, where surgical stimulus/stress or drug interactions (more than one drug used) are present.

In this observational study, the aim is to examine EEG signatures associated with the point of LOC in patients submitted to general anesthesia with the analgesic drug remifentanil and anesthetic drug propofol during neurosurgeries. For that, it was recorded raw EEGs while administering the drugs to 12 patients and assessing LOC. Time-varying spectrograms were computed to observe the dynamics of EEG oscillations during the induction of general anesthesia.

Materials and Methods

A. Clinical Data

The current observational study prospectively enrolled 16 patients from the Neurosurgery Service at Centro Hospitalar do Porto (Porto, Portugal). A total of 12 patients were included in the final analysis of data. Data were recorded from the beginning of the analgesic drug remifentanil administration until 10 minutes after LOC. LOC was accessed by observing the absence of any movement when hitting the patient's forehead.

Each patient received anesthetic induction with a remifentanil effect-site concentration (Ce) target of 2ng/mL or 2.5ng/mL. When the remifentanil Ce target is achieved, the propofol infusion started at 200mL/h (slow infusion) until LOC. At LOC, the propofol's Ce target was set to the value reached at LOC until intubation.

B. Experimental recordings and data processing

Before beginning the drug administrations, the patients' foreheads were treated with alcohol, and a BIS VISTA^{TM} monitoring system-specific electrode was placed. Raw EEG signals were acquired at a sampling rate of 128 Hz using a BIS VISTA^{TM} monitor. After transferring the raw EEG signal to a computer, the data were processed using MATLAB (MathWorks, Natick, Massachusetts, USA).

Raw EEG signals were band-pass filtered between 0.1 and 60 Hz before multitaper spectrograms were computed. From the multitaper spectrogram, the six EEG sub-bands were decomposed: gamma (25-40Hz), beta (12-25Hz), alpha (8-12Hz), theta (4-8Hz), delta (1-4Hz), and slow (0.1-1Hz) power.

C. Multitaper spectrograms

The spectrogram is a time-varying version of the power spectrum using consecutive windows of EEG data. The multitaper spectrogram is the concatenation of the Power Spectral Density (PSD) of the EEG data in small sliding windows with overlap. The overlap makes it possible to compute spectral estimates at a desired temporal resolution. The choice of the window length determines the spectral resolution of the spectral estimation. However, the window length choice also limits the time resolution of the spectrogram, by the uncertainty principle. Given data of length N and sampling interval Δ, computing the spectrogram representation based on multitaper spectral estimation [134] can be summarized as follows:

1. Estimate the time-scale on which the data can be assumed to be second-order stationery [135] (meaning that the Fourier transform of the autocovariance sequence is equivalent to the PSD and so the spectral density can be computed). Denote it by T and let $N = \frac{T}{\Delta}$.
2. Pick a spectral resolution R, such that $\alpha = \frac{N\Delta R}{2} \geq 1$.
3. Pick a sliding length $\tau \leq T$, and let $K = \frac{\tau}{T}N$.
4. Find the multitaper estimate of the PSD of the data at windows of length N, centered at time indices $n = \frac{N}{2}, \frac{N}{2} + K, \frac{N}{2} + 2K, \ldots$ until the entire data series is covered.

It is possible to construct the spectrogram based on a parametric spectral estimator [134]. At each window, assuming an autoregressive model, a parametric estimate of the spectral density can be obtained through model selection and fitting [134].

Here, the multitaper spectrograms of the EEG data were computed using the Chronux toolbox (http://chronux.org) as described elsewhere [136]. Multitaper parameters used window lengths of 6s with an overlap of 0.1s, a time-bandwidth product of 3, and 5 tapers.

Results

Twelve patients were included in this observational study.

Demographics for the 12 patients were: 57±13 years of age, 69±17 kg, 168±13 cm, 5 males, and 7 females. In Table 5.1 are presented the main results for all 12 patients regarding: the analgesic and the hypnotic concentrations at LOC, the time to LOC and the observations of the dynamics of EEG oscillations during induction of general anesthesia.

Table 5.1 Patient data regarding drug concentrations (Ce – Effect site concentration) required for loss of consciousness (LOC) and EEG spectrogram.

Patient	Remifentanil Ce at LOC (ng/mL)	Propofol Ce at LOC (µg/mL)	Time from starting propofol until LOC (min)	EEG spectrogram's observations at LOC
1	2.00	4.11	6.92	Gamma decrease Delta increase Alpha increase
2	2.39	5.26	3.55	Gamma decrease Delta increase Alpha increase
3	2.49	3.94	2.45	Gamma decrease Delta increase Alpha increase
4	2.50	3.82	2.26	Gamma decrease Delta increase Alpha increase
5	2.00	5.11	3.52	Gamma decrease Delta increase Alpha increase
6	2.49	3.64	2.28	Gamma decrease Delta increase Alpha increase
7	1.00	4.10	2.35	Gamma decrease Delta increase Alpha increase
8	2.10	5.41	4.12	Gamma decrease Delta increase Alpha increase
9	2.36	2.91	1.88	Gamma decrease Delta increase Alpha increase
10	2.49	6.07	3.65	Gamma decrease Delta increase Alpha increase
11	2.50	5.96	3.62	Gamma decrease Delta increase Alpha increase
12	2.00	6.17	4.15	Gamma decrease Delta increase Alpha increase

All patients presented a very similar behavior in the EEG spectrogram with a progressive decrease in gamma band and an increase in alpha and delta powers as the patients progress from conscious to unconscious states.

Figure 5.1 and Figure 5.2 show the results from two representative patients (Patient 8 and 9, respectively).

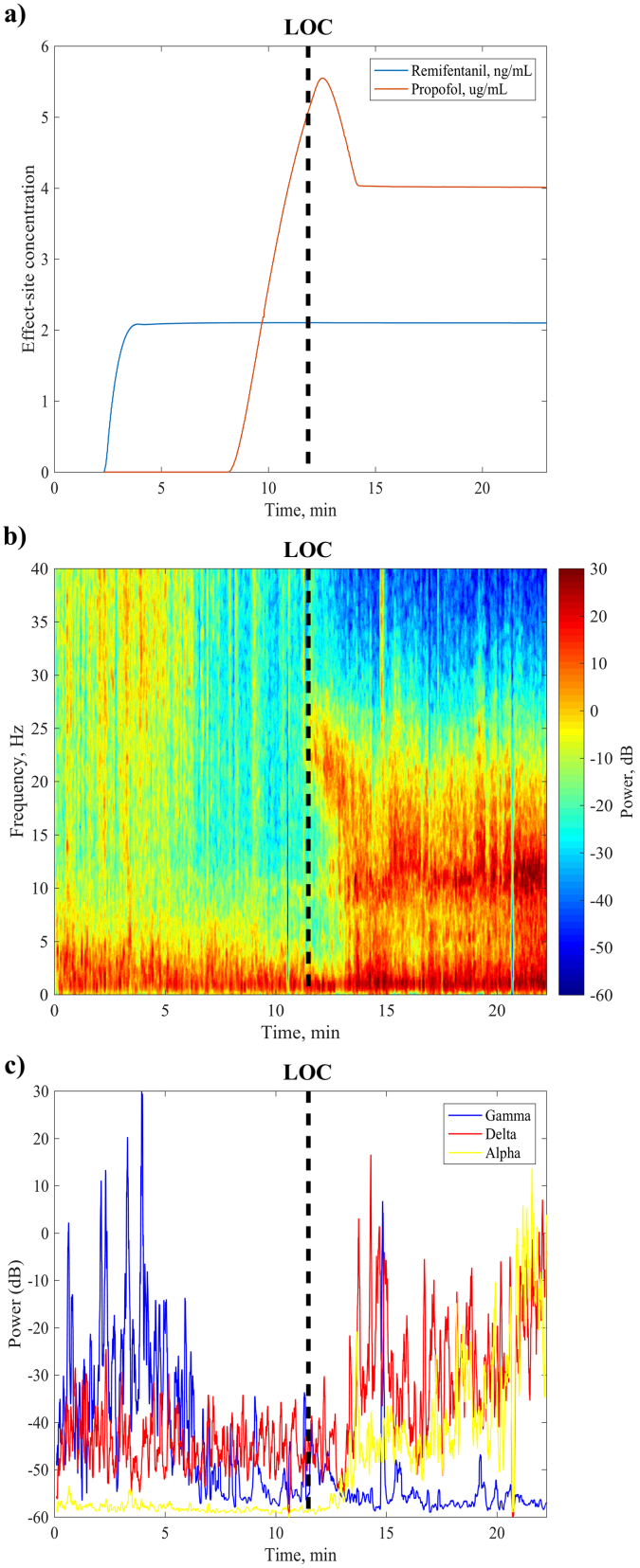


Figure 5.1 Dynamics from patient 8 during induction from remifentanil (Ce target of 2ng/mL) and propofol induced unconsciousness: a) Drugs concentrations aligned with respect to LOC; b) EEG spectrogram aligned with respect to LOC; c) Power in gamma (25-30Hz), delta (1-4Hz) and alpha (8-12Hz) bands aligned with respect to LOC.

As can be observed from Figure 5.1a), the induction started with remifentanil to a concentration target of 2.5ng/mL, followed by the slow infusion of propofol. When the anesthesiologist observed an absence of movement when hitting the patient's forehead, he/she stopped the infusion of propofol, which is identified as the moment of LOC. A continuous increase of the propofol Ce concentration still occurring until a peak of the effect-site concentration was reached. After this peak, the propofol Ce concentration decreased until the end of the study time (10 minutes after LOC). This patient took 1.88 minutes to enter the unconscious state, i.e., to achieve LOC. At LOC, the remifentanil and propofol Ce concentrations were 2.36ng/mL and 2.91μg/mL, respectively. The EEG spectrogram (Figure 5.1b) show a progressively diminishing in the gamma band and a rising in the delta and alpha bands as the patient transitions through the unconscious state. This was verified with the behavior of the decomposed waves in Figure 5.1c).

Concerning patient nine represented in Figure 5.2, similar results were observed.

There is a clear pattern in the way the EEG oscillations behave like the patient state shifts from conscious to the unconscious in 11 of the 12 patients. This pattern is similar even with a two-fold range in the required anesthetic propofol concentration to achieve LOC and different analgesic concentrations. Although the magnitude of these changes still needs to be quantified.

Conclusions and Future Work

In this paper, changes during the transition from consciousness to unconsciousness in patients submitted to general anesthesia with remifentanil and propofol were observed. As the patients progresses from conscious to unconscious, the observed EEG data states that gamma power decreases, and alpha and delta power increases. These results have not been previously shown in patients undergoing surgery.

In the future, it is intended to develop a dynamic state-space model framework for the simultaneous characterization of involuntary and monitored physiological dynamics during the gradual transition from consciousness to unconsciousness. Also, simultaneously acquiring three modalities of observations related to the onset of unconsciousness will be performed: behavioral responses, EMG activity, and EEG spectral power. Combining the information from all of these different types of observations, a robust and well-supported estimate for tracking the dynamic changes in a subject's wakefulness as they enter into the unconsciousness state can be created.

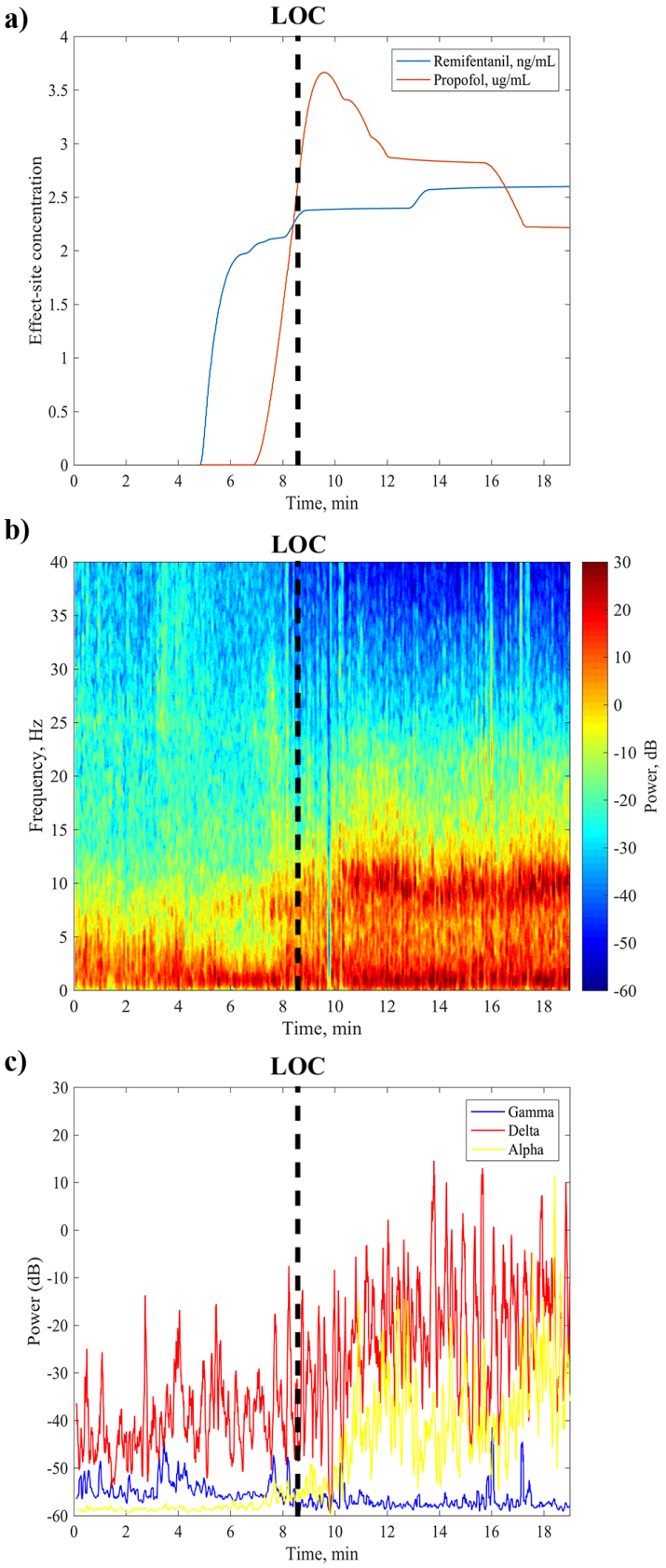


Figure 5.2 Dynamics from patient 9 during induction from remifentanil (Ce target of 2.5ng/mL) and propofol induced unconsciousness: a) Drugs concentrations aligned with respect to LOC; b) EEG spectrogram aligned with respect to LOC; c) Power in gamma (25-30Hz), delta (1-4Hz) and alpha (8-12Hz) bands aligned with respect to LOC.

5.2 Implementation of neural networks to frontal electroencephalography for the identification of the transition responsiveness/unresponsiveness during induction of general anesthesia

Ana Leitão Ferreira MSc, Sérgio Vide MD, Catarina S. Nunes PhD, João Neto MSc, Pedro Amorim MD, Joaquim Gabriel Mendes PhD

Abstract

Using bilateral frontal electroencephalography (EEG) and Deep Neural Networks (DNN), it was studied the induction phase of anesthesia with remifentanil and propofol to identify the exact moment of loss of responsiveness.

A clinical protocol was designed to allow for different clinical endpoints' characterization throughout the transition to unresponsiveness. Fifty (50) patients were enrolled in the study, and data from all was included in the final dataset analysis. While under a constant estimated effect-site concentration of 2.5 ng/mL of remifentanil, an 1% propofol infusion was started at 3.3 mL//h until loss of responsiveness. The level of responsiveness was assessed by an anesthesiologist every six seconds using a modified version of the Richmond Agitation-Sedation Scale (aRASS). The frontal EEG was acquired using a bilateral bispectral (BIS) sensor. EEG data were then split into 5-second epochs, and for each epoch, the anesthesiologist's classification was used to label the patient as responsiveness (no-LOR) or unresponsiveness (LOR). All 5-second epochs were then used as inputs for a Convolutional Neural Networks (CNN) to classify the segment as LOR or no-LOR.

The CNN successfully identified the transition from no-LOR to LOR, achieving 97.90 ± 0.07% accuracy on the cross-validation set.

Limitations of the study include the reduced number of patients in the CNN testing datasets. Preliminary results indicate that bilateral frontal EEG may contain useful information in assessing the responsiveness/unresponsiveness balance.

Keywords: anesthesia, propofol, remifentanil, loss of responsiveness, electroencephalogram, deep neural network, convolution neural networks.

Introduction

Detecting the exact moment of Loss of Responsiveness (LOR) during anesthesia induction represents a significant clinical endpoint of the brainstem's anesthetic effect. Propofol, the most widely used induction agent to induce unresponsiveness, is usually injected as a rapid bolus based on the patient's weight, resulting in a very fast LOR, which tends to be associated with overdosing [5]. This rapid loss of response makes it difficult to detect the exact moment at which it occurs, therefore precluding the use of this endpoint for drug titration.

The recommended propofol dose for the induction of General Anesthesia (GA) lies between 2 to 2.5 mg/kg injected at a rate of 40 mg every 10 seconds [137], which for a 70 kg adult results in the administration of 140 mg of propofol over 40 seconds (1260 mL/h if 1% propofol). With this technique, LOR occurs very rapidly on a scale of seconds, not allowing assessment of the clinical events during the transition from responsiveness to unresponsiveness. Alternatively, the administration of propofol at a slow-rate constant infusion [5][138][19] allows several endpoints to be observed, such as the closing of the eyes, loss of behavioral response, loss of response to verbal commands, and ultimately loss of corneal reflex (i.e. LOR). While this approach requires more time to obtain LOR, it offers the advantage of precisely detecting the propofol dose needed for the desired clinical endpoint. This would provide personalized information on anesthetic requirements and could help maintain an adequate level of anesthesia throughout surgery [79], ensuring safe and effective care and balancing the avoidance of intraoperative awareness [139][131][132] and overdose [133].

As propofol's end-target organ is the brain, one of the above-mentioned clinical endpoints might be based on electroencephalographic (EEG) features. Present-day "Depth of Anesthesia" (DOA) monitors, although routinely used during general anesthesia, were not designed to detect the moment of LOR and lack the temporal resolution to do so with precision [140]. This may lead to delayed LOR detection and subsequent excessive propofol administration.

Previous studies exploring novel approaches to EEG analysis have shown that Artificial Neural Networks (ANNs) achieved good discrimination between awake and anesthetized states [141][142][143]. However, these studies have not explored the use of ANN or any other neural network to detect the precise moment of LOR.

ANNs with a multilayer structure are called Deep Neural Networks (DNNs). Similar to ANNs, DNNs are composed of an input layer that accepts the independent external inputs and an output layer that generates predictions. Unlike ANNs, DNNs are composed of multiple hidden layers. Neurons in a hidden layer or output layer are connected to all neurons of the previous layer. Each neuron computes a weighted sum of its inputs and applies a nonlinear activation function to define each neuron's output. Common activation functions used in neural networks include the linear function, sigmoid, tanh, softmax and rectified linear unit (ReLU) function [145]. To achieve the best output, DNNs repeat constant learning and error correction.

Many published variants and combinations of DNNs have been published, with the most popular being Multilayer Perceptron (MLP), Autoencoders (AE), Convolutional Neural Networks (CNN) and Recurrent

Neural Network (RNN) [146]. Each of these DNNs computes losses in their own manner. Losses represent the difference between the true and the computed outputs. These losses are back-propagated to adjust the weights and are then trained to minimize the losses or to make the models more accurate.

DNNs are more reliable than ANNs and increase accuracy as we add more neuron layers before a certain amount of layers of the predictive power starts to decrease [147].

The main objective of this study is to investigate the possibility of applying DNNs to the raw EEG to determine the precise moment of LOR in the induction phase of anesthesia with propofol and remifentanil.

Material and methods

A. Patients and EEG Recordings

The EEG signals were recorded from 50 consecutive adult patients (60±14 years old, 22 women, 5 ASA I, 32 ASA II and 13 ASA III, 72.23±12.13 kg, and 163.0±9.27 cm) undergoing routine neurosurgical procedures under GA at Centro Hospitalar do Porto. After cleaning the skin, sensors from the bispectral index monitor (BIS VISTA™ v2.0, Medtronic, Ireland) were placed over the forehead of all patients to obtain the EEG signals (Figure 5.3). This study was conducted following institutional and Ethics Committee approval (Ref. 068-17 (062-DEFI/062-CES), Appendix C). Written informed consent was obtained from each patient.

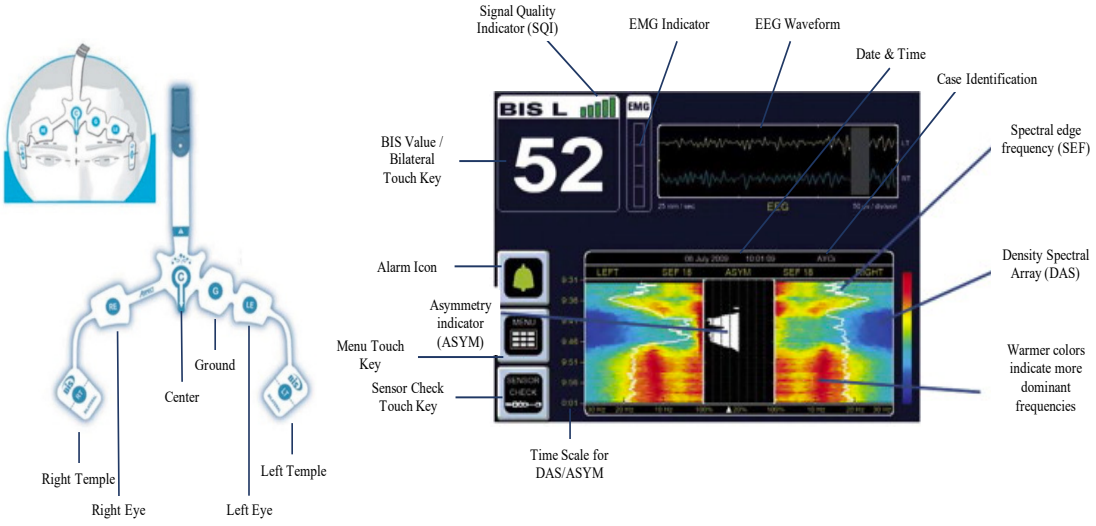


Figure 5.3 BIS Vista™ Bilateral Sensor and Vista Monitor®. Monitoring of the left hemisphere (BIS L). (Photos provided by Medtronic).

Standard practice for neurosurgical procedures consists of opioid-propofol anesthesia using a Target Controlled Infusion (TCI) system. In the operating room, after placement of standard monitor, the anesthesiologist started a TCI of remifentanil (Minto pharmacokinetic/pharmacodynamic - PKPD model [78]), at an effect-site concentration (Ce) target of 2.5 μg/mL, using a Fresenius Base Primea docking

station (Fresenius-Kabi, Bad Homburg, Germany). A bolus of 10 mg of lidocaine was administered locally to reduce the pain associated with propofol administration. One minute after the remifentanil pseudo-equilibration was achieved, an infusion of 1% propofol (Schnider PKPD model [28]) was started using the TCI enabled infusion system, in the TCI-View mode, at 3.3 mL/kg/h, until LOR, determined by the anesthesiologist. The anesthesiologist assessed the level of responsiveness every six seconds since the propofol infusion started, using an adapted version of the Richmond Agitation-Sedation Scale (RASS) [144], which we entitled by aRASS scale (Table 5.2). This scale was a modification of the RASS scale [144], described to measure agitation or sedation level of hospitalized patients, and we add the corneal reflex endpoint, yielding an adapted Richmond Agitation-Sedation Scale (aRASS). LOR, defined as a scale of -6 in the aRASS scale, was evaluated using a drop of sterile water to the cornea. The corneal reflex evaluation started only after the aRASS reached the -5 in aRASS score. After that, corneal stimulation with drop was evaluated every 6 seconds. If the patient's eyes blinked consensually, the reflex was intact. If only one eye blinked, the reflex was impaired, and if neither eye blinked, the reflex was absent.

Table 5.2 - The adapted Richmond Agitation-Sedation Scale (aRASS). Definition of seven anesthetic stages based on clinical signs. The main clinical signs of each state are referred, as well as the attributed a numerical scale.

Behavior	Descriptive	Score
Awake	Fully awake and alert	0
Drowsy	Not fully alert, but has sustained awakenings to voice (eye opening and eye contact)	-1
Light Sedation	Briefly awakens to voice (eye opening and eye contact)	-2
Moderate Sedation	Movement, but no eye opening or contact to voice	-3
Deep Sedation	No response to voice, but movement or eye opening to shaking and shouting	-4
Unarousable	No response to shaking and shouting, but still have corneal reflex	-5
Unresponsiveness	No corneal reflex	-6

At LOR, defined as -6 on the aRASS scale and indicated by the lack of corneal reflex to a sterile drop of water, the propofol infusion was stopped, and the dose and estimated Ce concentrations of propofol were noted. The TCI system was switched to effect-site TCI mode with a Ce concentration of propofol set to a 75% target of the Ce of propofol at LOR. At this point, no additional analgesic/opioid medication was given during induction. Propofol infusion was subsequently titrated to maintain BIS values between 40 and 60,

as recommended by the manufacturer. This will ensure an adequate hypnotic effect during GA while improving the recovery process.

B. EEG Analysis

Frontal raw EEG signals were acquired and recorded with a sample rate of 128 Hz using the BIS VISTA™ monitor (Figure 5.3), which allows to record and display of four channels of EEG, two from each side of the brain. It was considered the information corresponding to the two left-side channels of EEG (Left Temple and Left Eye). 2-channel raw EEG signals were pre-processed before subsequent analysis. The pre-processing of the data was kept to the minimum, consisting of a normalization to the mean and standard deviation of the raw EEG data. No filtering was applied.

Each EEG recording had a different duration because the time of surgery varied widely between patients. Thus, for each normalized EEG signal, 5-second epochs were extracted knowing that the low-end spectrogram signal analysis was around 0.2 Hz. Preliminary experimentation demonstrated worst model performances with frames less than 5-seconds and no significant improvements with more extended frames. Each EEG segment of 5-seconds resulted in a vector of 1280 values (5 seconds x 128 samples x 2 channels), which was labeled, by the anesthesiologists' clinical classification, using the aRASS scale, as well as labeled as a single value of estimated responsiveness (no-LOR: from aRASS=0 to aRASS=-5) or unresponsiveness (LOR: aRASS=-6). All 2-channel raw EEG pre-processed 5-second epochs were used as inputs to train the neural network. Output was the state of responsiveness expressed as 0 (no-LOR) or unresponsiveness, expressed as 1 (LOR).

Design and implementation of the prediction system

Experiments were performed based on a Convolutional Neural Network (CNN) configuration, a variant of the DNNs. CNNs significantly enhance the capabilities of the feed forward network by inserting convolution layers. Convolution layers are the layers where multiple filters, composed of small learned kernels, are applied to extract different features that predict the class to which each one belongs. In addition to the convolutional layers, CNNs accompany the convolutional layer using pooling layers, which are usually applied immediately after the convolutional layers. Pooling layers simplify and condense the information collected by the convolutional layer while maintaining the most important information. The result of this process feeds into a Fully Connected eural Network (FCN). The FCN portion of the CNN goes through its own backpropagation process to determine the most accurate weights. Each neuron receives weights that prioritize the most appropriate label. Finally, the neurons decide which label goes to the final classification.

To feed our CNN model, we used all 2-channel raw EEG (converted to a 1-D block) pre-processed 5-second epochs as inputs. A total of 28 786 frames were used to classify each segment as LOR or no-LOR. Each segment has dimensions 5 × 128 (samples) × 2 (channels) = 1280 samples. During each epoch, the CNN received batches of all the 28 786 frames, one of each of unresponsive and more than one of

responsive, to accommodate for the oversampling necessary for the balancing of the training. Model engineering consisted of iteratively adjusting the network architecture, i.e., number of convolutional layers, pooling layers, fully connected layers, and filters for each layer, along with parameter optimization.

The implemented CNN model was trained on an NVIDIA Titan X Pascal. The model was built using Python 3.7 [148] and Pytorch [149] on an Ubuntu server.

Performance analysis

After development of the DNN model was complete, the classification accuracy of the final DNN was evaluated. Hold-out validation is the standard for deep neural networks. Hold-out validation partitions the full dataset randomly into training and validation sets. Models are trained with different hyper-parameters on the training set, from which the model with the highest performance, given by the prediction accuracy on the validation set, is selected. In the experiments, 80% of the data was used to train, and 20% evaluated the model generated from the training set. Each evaluation set had 10 runs.

To understand the dependency on the data for such a small dataset, a cross-validation analysis was performed to evaluate how the results changed when selecting different cases for the validation set. The following assessments were considered to evaluation: Accuracy, Specificity, Precision, Recall, F_1, and Receiver Operating Characteristic (ROC). These assessments computed the accuracy and deviation to evaluate the feasibility and robustness of the DNN prediction model. Based on confusion matrix parameters can be calculated to check the performance of a classifier as follows:

- $Accuracy = \frac{TP+TN}{TP+TN+FP+FN}$
- $Specificity = \frac{TN}{TN+FP}$
- $Precision = \frac{TP}{TP+FP}$
- $Recall = \frac{TP}{TP+FN}$
- $F_1 = 2 \times \frac{Precision \times Recall}{Precision + Recall}$

Where TP (true positive) is the number of frames that the test declares as LOR's and they are truly LOR's; TN (true negative) is the number of frames that the test declares as no-LOR's and that are truly no-LOR's; FN (false negative) is the number of frames that the test declares no-LOR's and that in reality are LOR's; FP (false positive) is the number of frames that the test declares LOR's and that in reality are no-LOR's. F_1 is a measure of test accuracy and can be interpreted as a weighted average of precision and recall. In addition, the ROC curve illustrates the classifier performance by the graphical plot. The ROC curve is generated by plotting the TP rate against the FP rate.

Results

Raw EEGs from 50 patients were included in the analysis. Regarding drug infusion, at LOR, the estimated propofol and remifentanil Ce concentrations were 4.26±1.34 μg/mL and 2.5 ng/mL, respectively. According to the anesthesiologist's evaluation, the moment of LOR occurred in less than 3 minutes on average (min-max: 1.42 -3.68 minutes) after propofol infusion started.

Figure 5.4 shows an example of successive EEG signals for one single channel of one subject. Each row corresponds to a 5-second epoch and shows the effects of the increasing administration of propofol. The corresponding clinical classification given by the anesthesiologist (LOR or no-LOR) is presented. By merely observing the EEG signal, we are unable to conclude if the patient is still responsive or not.

After several trials adjusting the network's architecture, size, and hyperparameters of our implemented model, the resulting CNN is shown in Figure 5.6. The CNN consisted of nine 1-D blocks with convolutional layers followed by a 1024 FCN layer. The layers started with blocks of 16 convolutional filters and increased to blocks of 256 convolutional filters. Each block consisted of the convolutional layer itself, followed by a batch normalization layer and a ReLU activation. The last block contained an adaptive max-pooling layer, and a flatten operation to reduce the waveform's temporal dimension to 1. The last block activations were connected to a batch normalization, a dropout, and a fully connected layer. Batch normalization [150] was used to accelerate the neural network's training process and improve the stability of the model. Dropout was set to 0.5 to improve generalization. An Adam optimizer [151] with start learning set to 0.0001 and weight decay to 5e-5 was used, and the model was trained for 20 epochs. **Erro! A origem da referência não foi encontrada.** contains details about the stride, pool size, filter count, kernel size, and dropout rate. Finally, the output of the last layer was feed into an activation function, producing the resulting value of 0 or 1 according to LOR or no-LOR prediction. The applied activation function was the *LogSoftMax* in tandem with the negative *log*-likelihood loss function. The net output was dichotomous: 0 corresponding to no-LOR (or responsiveness) or 1 corresponding to LOR (or unresponsiveness). The predictions were then compared to the labels classified by the anesthesiologist, and the accuracy of the model was evaluated according to the correct pre- and post-LOR detection. Figure 5.5 shows the confusion matrices of classifier on 5-, 10- and 15-seconds varying time window. A time window of 15 seconds was chosen, so the algorithm would report three successive frames of no-LOR.

The best model was able to achieve 97.4% accuracy on the validation set when analyzing frame by frame. All the frames in the validation set were from cases never used in the training set, raising the difficulty level, and forcing generalization as desired. Given the size of the data, the approach was complemented with a stratified *k*-fold cross-validation method with k=10, i.e., the process was repeated with a different validation set to test for the biased that a small dataset could impose. Table 5.3 presents the cross-validation results, showing an average accuracy of 97.90 ± 0.07%. The best performance was achieved in run 4 from Set 9, in which accuracy, precision, recall, and F_1 were 97.99%, 96.21%, 97.05%, and 96.63%, respectively (Table 5.3). Since data from class 0 (no-LOR) and class 1 (LOR) are imbalanced, the CNN used special techniques to successfully deal with this issue by oversampling the less frequent ones

in the initial epoch. Micro- and macro-averages [152] were used to obtain ROC curves (Figure 5.7). The area under the curves (AUCs) of the CNN model's micro-and macro-averages were 0.99 and 0.98, respectively.

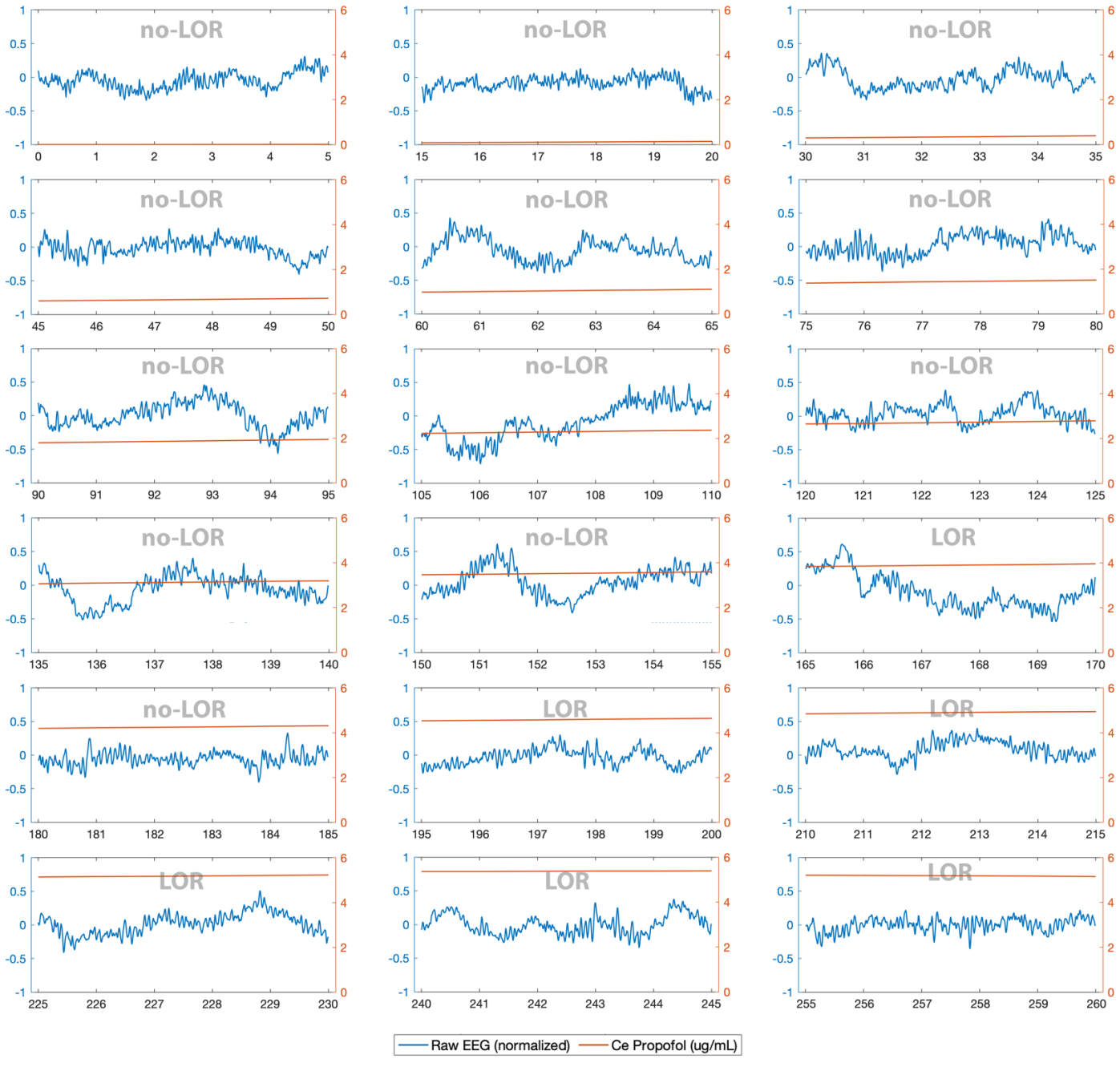


Figure 5.4 Example of successive 5-second electroencephalographic (EEG) epochs (blue lines) and the corresponding output (LOR or no-LOR) classified by the anesthesiologist. The estimated effect-site concentrations of propofol at each epoch are depicted in the graphic (red line).

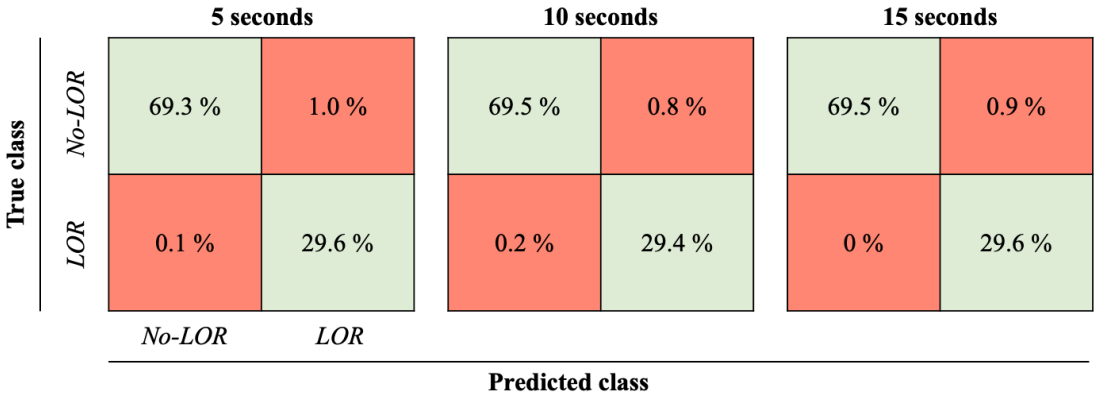


Figure 5.5 Confusion matrices on applying the classifier on Electroencephalographic (EEG) dataset using cross-validation and using a time window of 5, 10, and 15 seconds.

Table 5.3 Results of cross-validation (average over 10 runs).

Evaluation Set	Accuracy (%)	Precision (%)	Recall (%)	F_1 (%)
Set 1	97.94	96.19	96.91	96.55
Set 2	97.98	96.17	97.05	96.61
Set 3	97.91	96.09	96.91	96.50
Set 4	97.88	96.12	96.77	96.44
Set 5	97.99	96.21	97.05	96.63
Set 6	97.85	96.15	96.63	96.39
Set 7	97.76	96.12	96.35	96.23
Set 8	97.95	96.15	96.99	96.57
Set 9	97.82	96.19	96.47	96.33
Set 10	97.89	96.29	96.63	96.46
Maximum	**97.99**	**96.29**	**97.05**	**96.63**
Minimum	**97.76**	**96.09**	**96.35**	**96.23**
Mean	**97.90**	**96.17**	**96.78**	**96.47**
Standard Deviation	**0.07**	**0.06**	**0.25**	**0.13**

Discussion

The present study sought to determine whether a DNN applied to the raw EEG recorded from patients during opioid-propofol anesthetic procedures determines with precision the moment in which patients lose corneal reflex, i.e., loss of responsiveness or LOR, in the induction phase.

Using an anesthetic protocol of administering propofol at a slow-rate constant infusion led to the LOR to be reached on average 3 minutes after the induction started, which is only slightly more than the usual time intervals. However, considerable gains can be obtained by individualizing the amount of hypnotic to a clinical endpoint in the brainstem. It could help to prevent the effects of overdosing of the induction agent, such as arterial hypotension, the most common side effect and a deleterious one, given the evidence that even just 5 minutes of arterial hypotension negatively affect the outcome following surgery [8]. However, further studies are needed to establish more of these gains in terms of anesthesia maintenance stability and avoidance of undesired burst-suppression.

Assessing clinical endpoints of the brainstem, such as LOR, during GA is possible with EEG-based monitors, which become almost routine practice in the operating room. Exploiting that, we developed a CNN and applied the resulted model to the raw EEG recorded from patients during surgery. The CNN model A CNN was capablewas able to of identifying patients transitioning to LOR with a mean accuracy of 97.90 ± 0.07%, using unprocessed EEG waves., with a mean accuracy of 97.90 ± 0.07%, with only 15 seconds of delay. We consider this our approach constitutes an additional technique to the currently methods used in the daily clinical setting, where LOR is identified by the loss of response to verbal commands or mechanical stimulus, like (tapping on the forehead or squeezing of the shoulder muscles of the patient). Such methods imply that the anesthesiologist is stimulating the patient, causing arousal while simultaneously trying to induce unresponsiveness. We therefore hypothesized that automated EEG analysis could be a useful tool to detect the moment of LOR, especially using machine learning approaches, which have become indispensable for solving complex problems in most scientific fields [153]. Real time assessments of unprocessed EEG by the clinician during induction might be too cumbersome and could lead to inaccurate interpretations regarding the detection of the typical patterns.

There have been some studies so far that have used machine learning techniques to improve anesthesia delivery. Ortolani et al. [141] used an ANN to integrate thirteen EEG features to assess the level of anesthesia. Jiang et al. [142] analyzed EEG signals from 64 patients under different anesthetic protocols (55 with sevoflurane and desflurane and only 9 with propofol) using Sample Entropy (SE) analysis. The calculated signals from the SE analysis were used to train an ANN model, that performed accurately in discriminating between the awake and unresponsive state. Liu et al. [154] also proposed a method based on SE analysis and the Random Forest method for estimating the level of anesthesia through EEG signals. First, the SE feature derived from EEG signals distinguished the different stages for anesthesia. Second, three typical regression models, Support Vector Machine (SVM), ANN, and Random Forest were applied to the trained dataset dash. The results exhibited high accuracy for the estimation of this level (up to 73.0%). Shalbaf et al. [155] proposed an automated method for assessing anesthesia depth consisting of extracting

features from the SE and permutation entropy of the EEG signal. The extracted features were then used as inputs for an ANN, which was a data processing system based on the structure of a biological nervous system. The experimental results indicated that an overall accuracy of 92.4% could be obtained during propofol and desflurane anesthesia in 129 patients to distinguish between awake and general anesthesia. In another work, Shalbaf et al. [30] also used multiple features, including fractal, spectral and entropy from EEG signal to track anesthetic level. These features were feed to a neurofuzzy classification algorithm, based on fuzzy rules, whose accuracy on classifying EEG data into awake and general anesthesia states in 50 patients with propofol and volatile anesthesia was 93%. Gu et al. [13] used multiple EEG-based features, including frequency domain and nonlinear features as the inputs of ANN to estimate different anesthetic states within a dataset of 16 patients anesthetized with propofol. A high classification accuracy was obtained in detecting awake, light, and general anesthesia states; however, the proposed method exhibited a poor performance (14%) in detecting the deep anesthesia state. Guo et al. [31] used a wavelet transform method to analyze the anesthesia monitoring EEG signals and to cluster the extracted features to estimate DOA.

In these previous studies, good accuracy results were obtained for level of anesthesia tracking using EEG features as inputs in the neural networks. This was expected since the frontal EEG monitors are validated for measuring DOA 32 during surgery or sedation in steady state and slow transitions [32], and EEG energy band shifts are well described in these stages [33]. However, none of the above studies explored the possibility of using CNNs to detect the exact moment of LOR during anesthesia induction. Further, none of these studies used unprocessed EEG as direct inputs in their analysis.

Limitations

Regardless our preliminary results, a larger amount of data is necessary to train and test the neural network. Future research should focus on the collection of hundreds of new EEG labeled cases that can be used to re-train the model and improve accuracy even further, in terms of consistency and confidence interval levels. More research is also needed to study the impact of remifentanil on such a system, as well as with different anesthesia protocols with other drugs. We believe that our developed CNN model would be valid outside the combination opioid-propofol and anesthesia protocol. It used the raw EEG signal and the information it contains (effect of the central nervous system), therefore the amount of drug of infusion profiles should not change the performance. This is valid with other anesthetic drugs that affect the central nervous system in similar ways, monitors such as BIS or SedLine [160][161], also use processed EEG and work well for maintenance of anesthesia.

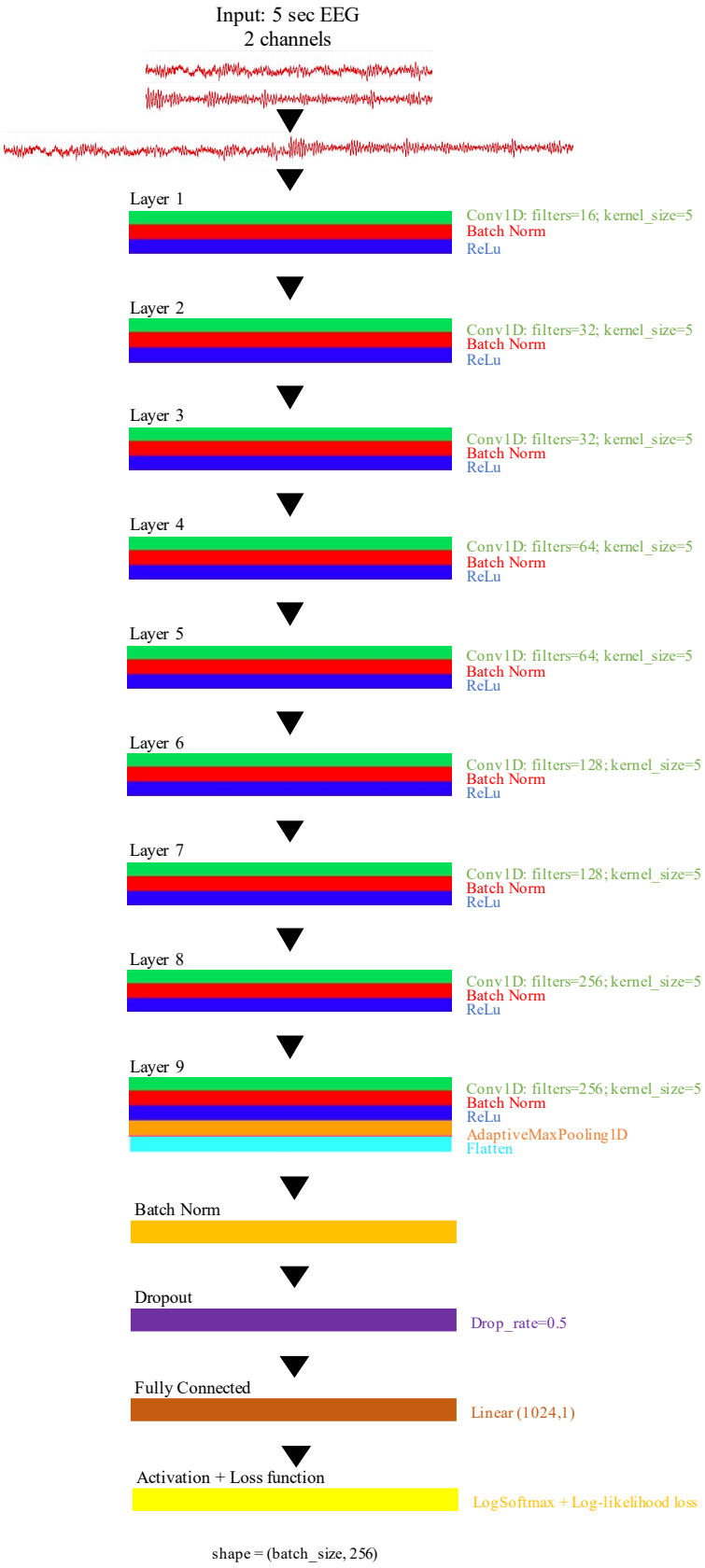


Figure 5.6 Architecture of the convolutional neural network (CNN). The electroencephalographic (EEG) input shape has dimensions 5 x 128 (samples) x 2 (channels) = 1280; the output of the net is dichotomous: 1 (LOR) or 0 (no-LOR). Stochastic optimization was realized using Adam [151] with learning rate=0.0001, and decay=5e-5. As the activation function, the *LogSoftMax* was used.

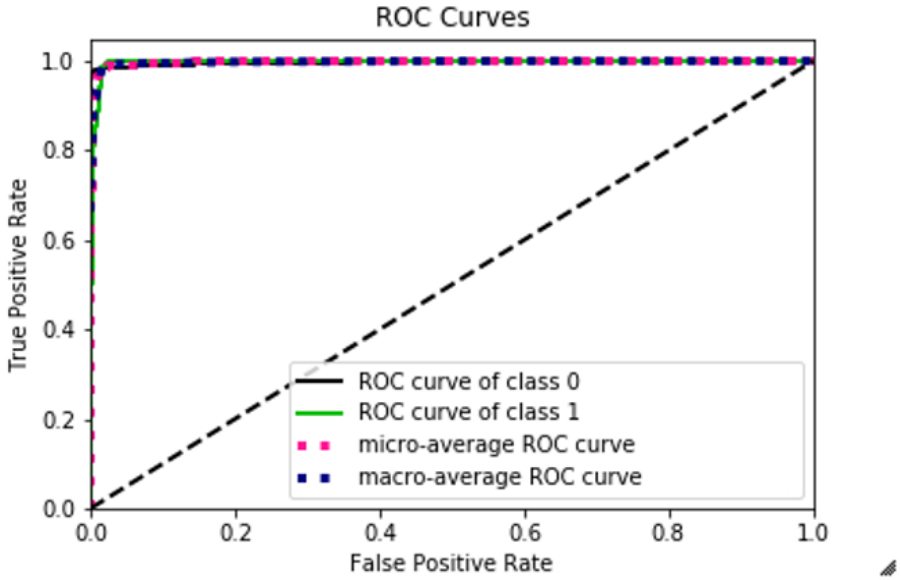


Figure 5.7 Performance of the Deep Neural Network (DNN) model in the test-set of the electroencephalography (EEG). Micro-average area under the curve and macro-average area under the curve are presented by receiver operation characteristics (ROC) curves.

During our clinical approach of general anesthesia, in order to assess the levels of sedation/anesthesia, anesthesiologists continued to stimulate the patient while trying to induce unresponsiveness. This seems counterintuitive but we believe that methods such as ours could replace that in the future.

Another constraint of our work was the choice of a 15-second time window so the algorithm would report three successive frames of unresponsiveness. We are convinced that, once we have a larger amount of data, we would achieve a similar model performance with just 5 seconds. A time window of less than 5 seconds is likely to be worst because EEG frequencies which are clinically relevant may be lost.

Conclusion

By analyzing bilateral frontal EEG during anesthesia with neural networks, we determined that there is enough relevant information to detect the state of unresponsiveness during the transition from responsiveness to unresponsiveness. The best results were obtained with a DNN, more specifically a CNN. DNNs became popular recently because large scale datasets with millions of diverse images became available and faster computer implementation was made available to public. Also, over the years, training algorithms and network architectures became more improved [159]. We implemented Oour developed approach was implemented on an internal cloud, which is now being used in real-time during medical procedures.

A similar approach with CNN may be used in the future to predict changes in the state of LOR during maintenance of anesthesia, as well as to differentiate between different levels of anesthesia depth, which would help to identify the possibility of arousal during surgery. We also intend to add other variables to feed the neural network, such as heart rate, blood pressure and electromyography. Additionally, we plan to use different EEG equipment for additionally robustness.

6 ELECTROMYOGRAPHY IN THE DETECTION OF LOSS OF CONSCIOUSNESS

This chapter is divided in two main sections, section 6.1 presenting a study developed to clinically identify the moment of loss of responsiveness and compare it with the electromyographic records of electrically evoked blink reflex by using neurophysiologic-derived parameters. Section 6.2 presents a developed study to evaluate the performance of the features extracted from the electromyographic records of electrically evoked blink reflex to predict the level of anesthesia during induction.

The study described in the first section resulted in one paper accepted for publication in Journal of Clinical Monitoring and Computing:

i. Electromyographic assessment of blink reflex throughout the transition from consciousness to unresponsiveness during induction with propofol and remifentanil.

The study presented in the second section resulted in one paper accepted for publication in Biomedical Engineering Online Journal:

i. Performance of blink reflex in patients during anesthesia induction with propofol and remifentanil: Prediction probabilities and multinomial logistic analysis.

This chapter is organized as follows:

6.1 Electromyographic assessment of blink reflex throughout the transition from consciousness to unresponsiveness during induction.

6.2 Performance of EMG-derived parameters from blink reflex: prediction probabilities and multinomial logistic analysis.

6.1 Electromyographic assessment of blink reflex throughout the transition from consciousness to unresponsiveness during induction

Ana Leitão Ferreira MSc, Sérgio Vide MD, João Felgueiras MSc, Márcio Cardoso MD, Catarina Nunes PhD, Joaquim Mendes PhD, Pedro Amorim MD

Abstract

General anesthesia is a reversible drug-induced state of altered arousal characterized by loss of responsiveness due to brainstem inactivation. Precise identification of the moment in which responsiveness is lost during the induction of general anesthesia is extremely important to provide information regarding an individual's anesthetic requirements and help intraoperative drug titration.

To characterize the transition from responsiveness to unresponsiveness more objectively, it was studied neurophysiologic-derived parameters of electromyographic records of electrically evoked blink reflex as a means of identifying the precise moment of loss of responsiveness.

Twenty-five patients received a slow infusion of propofol until loss of corneal reflex while successive blink reflexes were elicited and recorded every 6 seconds. The level of anesthesia was assessed using an adapted version of the Richmond Agitation-Sedation Scale. Different variables of the blink reflex components were calculated and compared to the adapted version of the Richmond Agitation-Sedation score and the estimated effect-site propofol concentration.

Baselines of the blink reflex responses were similar to those in literature. After propofol infusion started, the most susceptible component of the blink reflex to propofol was R_2 (EC_{50}=1.358 (95% CI: 1.321, 1.396) μg mL^{-1}) and the most resistant was R_1 (EC_{50}=3.025 (95% CI: 2.960, 3.090) μg mL^{-1}). Most of the patients (24 out of 25) lost the R_1 component when they were still responsive to shaking and shouting and corneal reflex could be elicited clinically (time=102.48±33.00 seconds). Habituation was present in R_2 but not in R_1. The R_1 component of the blink reflex was found to have a strong correlation with the adapted version of the Richmond Agitation-Sedation Scale, with amplitude correlating better than areas (ρ=-0.721 (0.123) versus ρ=-0.688 (0.165)). It was found a strong correlation between the R_1 component with the estimated propofol effect-site concentration, with amplitude correlating better than areas (ρ=-0.838 (0.113) versus ρ=-0.823 (0.153)) and between the clinical scale and the propofol concentration (ρ=0.856 (0.060)). The area and amplitude of the R_1 component showed to be indicators of predicting different levels of anesthesia (P_k=0.672 (0.183) versus P_k=0.709 (0.134)) and these are connected to the propofol concentrations (P_k=0.593 (0.10)).

Results suggest that electrically evoked blink reflex could be used during the induction of anesthesia as a surrogate of the Richmond Agitation-Sedation Scale to provide an objective endpoint as far as a -4. At this point, at the moment of loss of R_1, the propofol infusion may be stopped, as overshooting increases slightly the effect-site concentration afterward and eventually reaching loss of responsiveness. If the desired target is not achieved, the infusion can then be resumed.

Keywords: Personalized anesthesia, propofol, blink reflex, electromyography, loss of responsiveness, monitoring.

Introduction

To induce patient unconsciousness/unresponsiveness, anesthesiologists use a variety of different drug combinations; however, synergisms and inter-patient variability may lead to different dose requirements. Precise identification of the moment of loss of responsiveness during general anesthesia induction would allow for the determination of the amount of anesthetic that each patient requires in a given situation. This would provide personalized information on anesthetic requirements and could help maintain an adequate level of anesthesia throughout surgery [79], ensuring safe and effective care and balancing the avoidance of intraoperative awareness [139][131][132] and overdose [133].

Propofol is the most widely used intravenous hypnotic drug for inducing loss of responsiveness and is also used for the maintenance of general anesthesia. Despite its usefulness in several clinical settings, propofol exhibits a dose-dependent relationship with hemodynamic instability, with events such as hypotension and bradycardia increasing as propofol concentration increases during induction [162]. These adverse effects are generally proportional to the dose and rate of administration [163] but slow infusion while titrating for the desired clinical endpoints may reduce them.

Determining which endpoint to use for anesthesia induction with propofol may be chosen based on its pharmacological effects. After propofol is administered intravenously, it reaches multiple sites in the cerebral cortex, brainstem, and thalamus, subsequently altering neurotransmission [26]. This is a continuous process, and as the hypnotic drug concentration is increased in these sites, individuals gradually transit from wakefulness to unresponsiveness [164]. Surrogates of this hypnotic effect can be evaluated by carefully assessing the different stages patients go through until loss of responsiveness. Most of the commonly used clinical endpoints reflect both cortical and brainstem functions. Determining the moment of loss of behavioral responsiveness (LOBR) to stimulation may reflect cortical activity and occurs because hypnosis renders patients unable or unwilling to interact with their external environment [164]. Classifying the adequacy of the hypnotic effect based on the cortical function is possible by using, for example, the Richmond Agitation-Sedation Scale (RASS) [144]. The RASS is a score that ranges from 0 (alert and calm) to -5 (unarousable) and includes endpoints such as unresponsiveness to name calling, absence of eye-opening to stimulation or loss of response to shaking and shouting.

Another possibility for assessing propofol effect, as it has a profound effect on nerves originating in the brainstem, is the use of brainstem reflexes as clinical endpoints [165], namely the blink, corneal, oculocephalic, gagging and pupillary light reflexes [7].

Blink and corneal reflexes can be elicited by a light touch of the eyelids or cornea, resulting in a response that is usually qualitatively appraised and can be observed clinically. Recording the electromyographic (EMG) activity from the orbicularis oculi, however, provides quantitative information of the reflex circuit. The most commonly used sensory stimulus for eliciting the blink reflex is a brief electrical shock applied to the supraorbital nerve. The reflex response to that stimulus consists of two separate components: R_1 and subsequently R_2. The two responses have different pathways in the brainstem [166]. The R_1 response relates to an oligosynaptic pontine reflex, whereas R_2 is relayed through a more complex route including many interneurons in the pons and lateral medulla [167]. The reflex circuit descends through the spinal trigeminal tract and enters a polysynaptic chain of interneurons in the lateral reticular formation and finally projects to the facial motoneurons bilaterally.

Thus, with the present study, it was intended to evaluate whether neurophysiologic-derived parameters of EMG records of electrically evoked blink reflex are useful in identifying the moment of loss of responsiveness determined with a modified version of the RAAS scale, in the continuum to unconsciousness.

Methods

A. Patients

After Institutional Review Board and Ethics Committee approval (Ref. 068-17 (062-DEFI/062-CES), Appendix C), twenty-eight consecutive adult patients undergoing routine neurosurgical procedures under general anesthesia at Centro Hospitalar do Porto were considered for this study. Period of enrollment was from June 2018 to July 2018. The anesthesiologist in charge of the room was the same over the one-month period of the study. All patients gave written informed consent.

Exclusion criteria were: baseline RASS [144] lower than 0 or Bispectral Index<90 before induction and significant cardiovascular, renal, hepatic or respiratory pathology and obesity (BMI>35kg/m^2).

B. Anesthesia Protocol

In the operating room, after placement of standard monitor and an intravenous line in the dorsum of the hand, an infusion of a balanced electrolytic solution was started at 6mL/kg/h. The anesthesiologist would then start a target control infusion (TCI) of remifentanil (Minto PKPD model) [29][78], using a Fresenius Base Primea docking station (Fresenius-Kabi, Bad Homburg, Germany), at an effect-site concentration (Ce) target of 2.5 ng/mL. A bolus of 10 mg of lidocaine was administered to reduce the pain associated with propofol administration. One minute after the remifentanil pseudo equilibration was achieved, baseline blinks were recorded and, then, an infusion of 1% propofol (Schnider PK-PD model) [14] was started using a TCI enabled infusion system, in the TCI-View mode, at 3.3 mL/kg/h until loss of responsiveness, determined by the anesthesiologist. This slow velocity of infusion during induction enables a careful titration of the minimum amount of propofol required for loss of responsiveness. Once unresponsiveness was reached, the propofol infusion was stopped, the estimated propofol Ce concentration was noted and the TCI system was switched to effect-site TCI mode with a Ce of 75% of that at loss of responsiveness. At this point, no additional analgesic/opioid medication was given during induction. Propofol infusion was subsequently titrated to maintain BIS between 40 and 60 (BIS Vista^{TM} monitor – Medtronic, Ireland). The study was terminated just before tracheal intubation.

C. Electromyographic stimulations and recordings

The electromyographic stimulations and recordings were conducted with the VikingQuest^{TM} neurophysiological device (VikingQuest, Nicolet, WI, USA) at 200 ms total sweep time with a sample rate of 10 kHz. High pass filter was applied with a cutoff frequency of 20 Hz. Before induction of anesthesia and prior to electrode application, all the patient's head skin surfaces were cleaned with an exfoliating agent. Surface electrodes (1.4 cm^2) coated with conductive paste (electrode impedance <8 kΩ) were applied to stimulate and record the electromyogram from the right orbicularis oculi muscle. The supraorbital nerve was stimulated transcutaneously with a bipolar electrode with the cathode placed beneath the eyebrow over

the supraorbital notch and the anode placed above the eyebrow (interelectrode distance 2 cm). The supraorbital nerve was electrically stimulated with a duration of 0.1 ms at 0.16 Hz. With regard to the recording electrodes, the recording electrode was placed in the middle of the inferior rim of the orbit; the reference halfway on the eye-ear line and the ground electrode was placed on the cheek or on the shoulder of the patient (Figure 6.1).

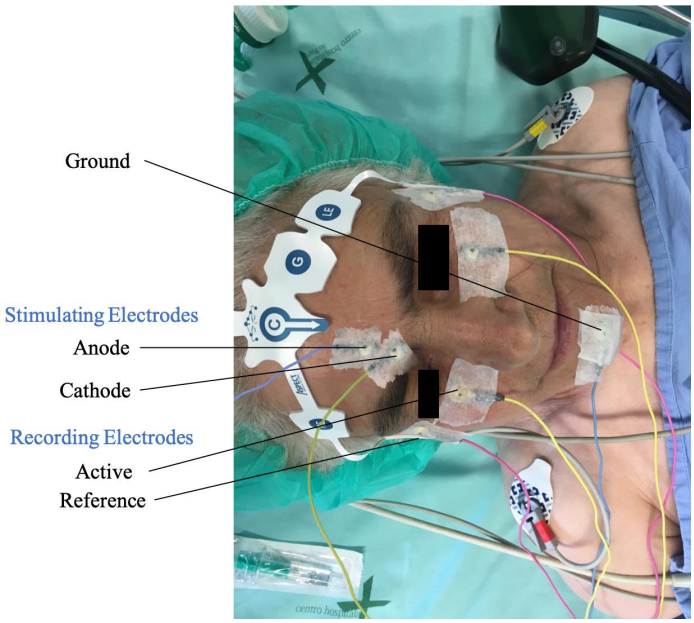


Figure 6.1 Patient with the positioned electrodes for stimulation and recording of electrically evoked blink reflexes in the orbicularis oculi muscle.

The signals were stored in the VikingQuest software provided by the manufacturer. The raw data was exported to a personal computer to be treated and analyzed in MATLAB®.

The electromyography records of an electrically evoked blink reflex showed at least two components (R_1 and R_2 components). The first or early response (R_1) is brief and occurs after a latency of approximately 10 ms on the side of stimulation [168]. The second response, (R_2) has a latency of approximately 30 ms, is bilateral and more prolonged in time [168]. The R_2 response causes the actual contraction of the orbicularis oculi muscle [168]. The optimal stimulus intensity was sought by gradually increasing the current until visual observation of the EMG showed that, in the presence of a clearly visible R_1 component, the R_2 component reach its maximum amplitude [169].

D. Assessment of levels of responsiveness

The level of responsiveness was assessed every six seconds using an adapted version of the RASS score [144], entitled aRASS and described in Table 6.1. This scale is a modification of the RASS scale [144], with the addition of the corneal reflex endpoint, yielding an adapted Richmond Agitation-Sedation Scale (aRASS). LOBR, defined as a scale of -5 in the aRASS scale, was assessed by tapping in the patient's forehead. Loss of corneal reflex (LOCR), defined as a score of -6 in the aRASS scale was evaluated, after the aRASS reached a score of -5, using a drop of sterile water to the cornea. Hereafter, this evaluation was intercalated with electrical stimulations at 6 seconds intervals. If the eyes blinked concomitantly, the reflex

was intact. If only one eye blinked, the reflex was impaired, and if neither eye blinked, the reflex was absent.

Baseline blink reflexes and evaluation of the aRASS scale were recorded several times before propofol was administered. Patients then received propofol and four successive blink reflexes were elicited and recorded concurrently. After an interval of 6 seconds another four successive blink reflex stimuli were elicited and recorded continuously until LOCR was achieved.

Table 6.1 The adapted Richmond Agitation-Sedation Scale (aRASS). Definition of seven anesthetic stages based on clinical signs. The main clinical signs of each state are referred, as well as the attributed a numerical scale.

Behavior	Descriptive	Score
Awake	Fully awake and alert	0
Drowsy	Not fully alert, but has sustained awakenings to voice (eye opening and eye contact)	-1
Light Sedation	Briefly awakens to voice (eye opening and eye contact)	-2
Moderate Sedation	Movement, but no eye opening or contact to voice	-3
Deep Sedation	No response to voice, but movement or eye opening to shaking and shouting	-4
Unarousable	No response to shaking and shouting, but still have corneal reflex	-5
Unresponsiveness	No corneal reflex	-6

E. Blink reflex parameters

In this study, the 6 second interval between the four stimuli was chosen so habituation was minimal [170] but could still provide the temporal discrimination typically used in a clinical setting to determine LOBR in the Departamento de Anestesia do Centro Hospitalar do Porto. The mean of the four successive values was used to calculate the response variables (maximum amplitudes, latency, duration and areas under the curves R_1 and R_2). Latency, duration, area under the curve, that is, the mathematical integral of the absolute value of the raw EMG signal, and amplitudes of the R_1 and R_2 components from the electromyographically evoked blink reflexes were measured using the marker tool of the EMG system. An expert neurophysiologist put markers in place after the session took place. Latencies and durations were expressed in milliseconds (ms), area under the curves was expressed as microvolts x millisecond (μV.ms) and amplitudes in microvolts (μV).

It was considered LOR_1 (Loss of R_1 component) and LOR_2 (Loss of R_2 component) as the moments when R_1 and R_2 components were last seen in the EMG signal after an electrically evoked blink reflex. LOBR was defined as the moment at which patients lose behavioral responsiveness, i.e., when patients have no response to shaking and shouting. LOCR was defined as the moment at which patients lose corneal reflex.

F. Statistical Analysis

Graphical analysis of data preceded formal statistical analysis. The prediction probability (P_k) was used to test the capability of the response variables of the blink reflex to predict the aRASS and the estimated propofol Ce concentrations. P_k is a non-parametric correlation suited to ordinal variables and can accommodate variable scales having any degree of coarseness or fitness, which ranges from 0 to 1. A value of P_k=0.5 means that the indicator correctly predicts the anesthetic depths only 50% of the time, i.e., no better than a 50:50 chance. A value of P_k=1 means that the indicator predicts the anesthetic levels or the concentrations correctly 100% of the time. P_k was calculated for each patient, and an average of these P_k's was then calculated (group P_k). P_k was computed from Sommer's measure of association in the SPSS software program (IBM SPSS version 24.0 Il, USA). The average of individual Spearman's rank correlation coefficients (group ρ) was also calculated.

A sample size calculation was performed considering the results previously obtained by Mourisse et al. [171] [EC_{50} (LOBR)=2.44 (2.17-2.79) μg/mL *vs* EC_{50} (LOR_1)=2.82 (2.48-3.22) μg/mL *vs* EC_{50} (LOR_2)=1.58 (1.39-1.79) μg/mL] [18]. In their study, 20 pairs/patients were used. In the present study, since an opioid was present at induction and considering a 20% exclusion rate, a final sample size of 25 patients was established.

To investigate a relationship between the estimated Ce concentration of propofol and the loss of blink reflex components (LOR_1 and LOR_2), loss of behavioral responsiveness (LOBR) and loss of corneal reflex (LOCR), a logistic regression model was used, since the dependent variable reflects an underlying quantitative variable. The function used in the logistic transformation was the natural logarithm of the odds ratio. Thus, EC_{50} was obtained, representing the concentration of propofol at which 50% of the effect was observed and the Hill's slope, representing the steepness of the curve, and their 95% confidence limits (GraphPad Prism version 7.0a).

Habituation was expressed as the percentage decrease of the area of the reflex component between the first and fourth blinks. Differences between the first and the fourth blinks were evaluated by Student's t-test for paired data after Kolmogorov-Smirnov test (IBM SPSS version 24.0 Il, USA).

The Shapiro-Wilk test was used to test whether the data were normally or non-normally distributed. If normally distributed, the data were compared using a paired two-sided t-test, whereas if the data were non-normally distributed, a Wilcoxon signed ranks test was used. Comparison of the correlation coefficients and differences between effective values and curve estimates were evaluated by Bonferroni's corrected Student's t-test, for paired or unpaired data, when appropriate (IBM SPSS version 24.0 Il, USA).

Data are presented as mean ± standard deviation, unless stated otherwise. A p-value inferior to 0.05 was considered statistically significant (* $p<0.05$, ** $p<0.001$).

Results

Data from twenty-eight patients were analyzed. In 3 patients low quality EMG signals or abnormal baseline measurements (the baseline latencies of R_1 were longer (>3SD) than the reference values [172][173]) were present and these patients were excluded from the study. Twenty-five patients were considered for the analysis, with demographics as follows: 61±13 years old, 71.68±11.59 kg, 162.44±8.89

cm, 1 ASA I, 18 ASA II, 6 ASA III, 9 males and 16 females. No patient had cardiovascular or respiratory problems. All patients reached -6 in the aRASS.

The supraorbital nerve was stimulated with 26±5 mA, a well-accepted intensity by the patients [174]. Baseline values for all patients were determined. The mean baseline value of the latency of R_1 was 10.69±0.98 ms and R_2 38.16±7.25 ms. The baseline value of the duration of R_1 was 9.16±1.43 ms and R_2 32.41±10.11 ms. The baseline value of the amplitude of R_1 was 405.38±221.71 µV and R_2 416.68±193.61 µV. The baseline value of the area of R_1 was 1173.58±505.78 µV ms and R_2 2440.43±1356.16 µV ms. Figure 6.2 shows an example of a baseline response from one patient.

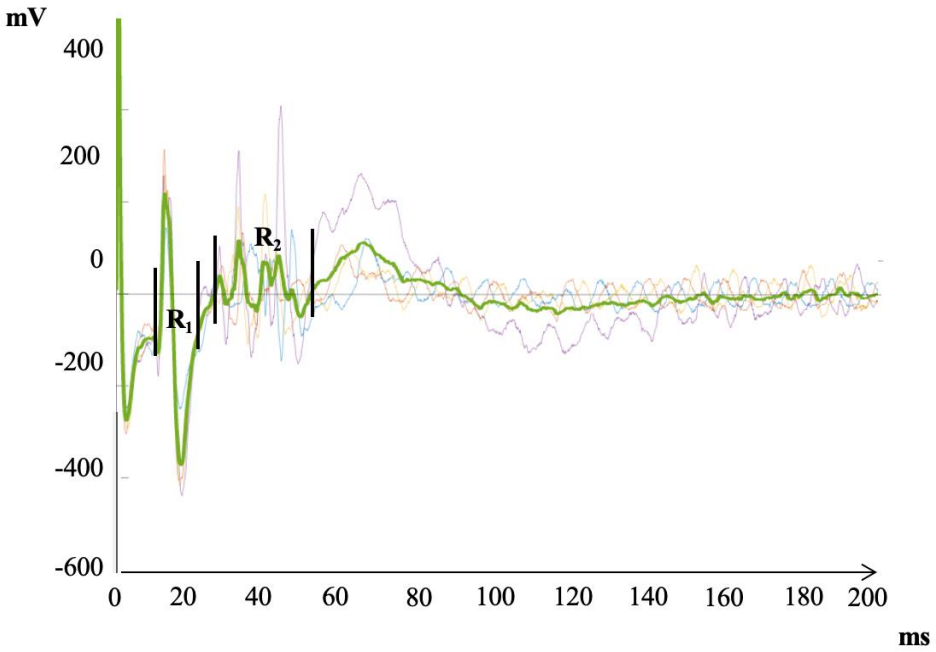


Figure 6.2 Example of an electromyographic record of an electrically evoked blink reflex before the infusion of propofol started (baseline). The highlighted line represents the average response from four consecutive blink reflex responses. Vertical lines mark the beginning and end of the individual components (R1 and R2), these lines were used to calculate latency, duration, area, and amplitude. These lines were marked by an expert neurophysiologist at the end of the session, using the marker tool of the VikingQuestTM neurophysiological device.

After the propofol infusion was started, areas and amplitudes of R_1 and R_2 decreased gradually towards zero. Figure 6.3 illustrates recordings obtained in one patient during propofol administration. The progression of the events for all patients is presented in Figure 6.4.

Table 6.2 shows the results of the times at which LOR_1, LOR_2, LOBR and LOCR occurred. The average estimated Ce concentrations of propofol and the aRASS score at those moments are also presented. With the exception of one patient, the corneal reflex (-6 in aRASS) was still present after LOR_1 disappeared. In 2 patients LOBR was equal to LOR_1, and in only 1 patient LOCR=LOR_1. All patients were responsive at LOR_2.

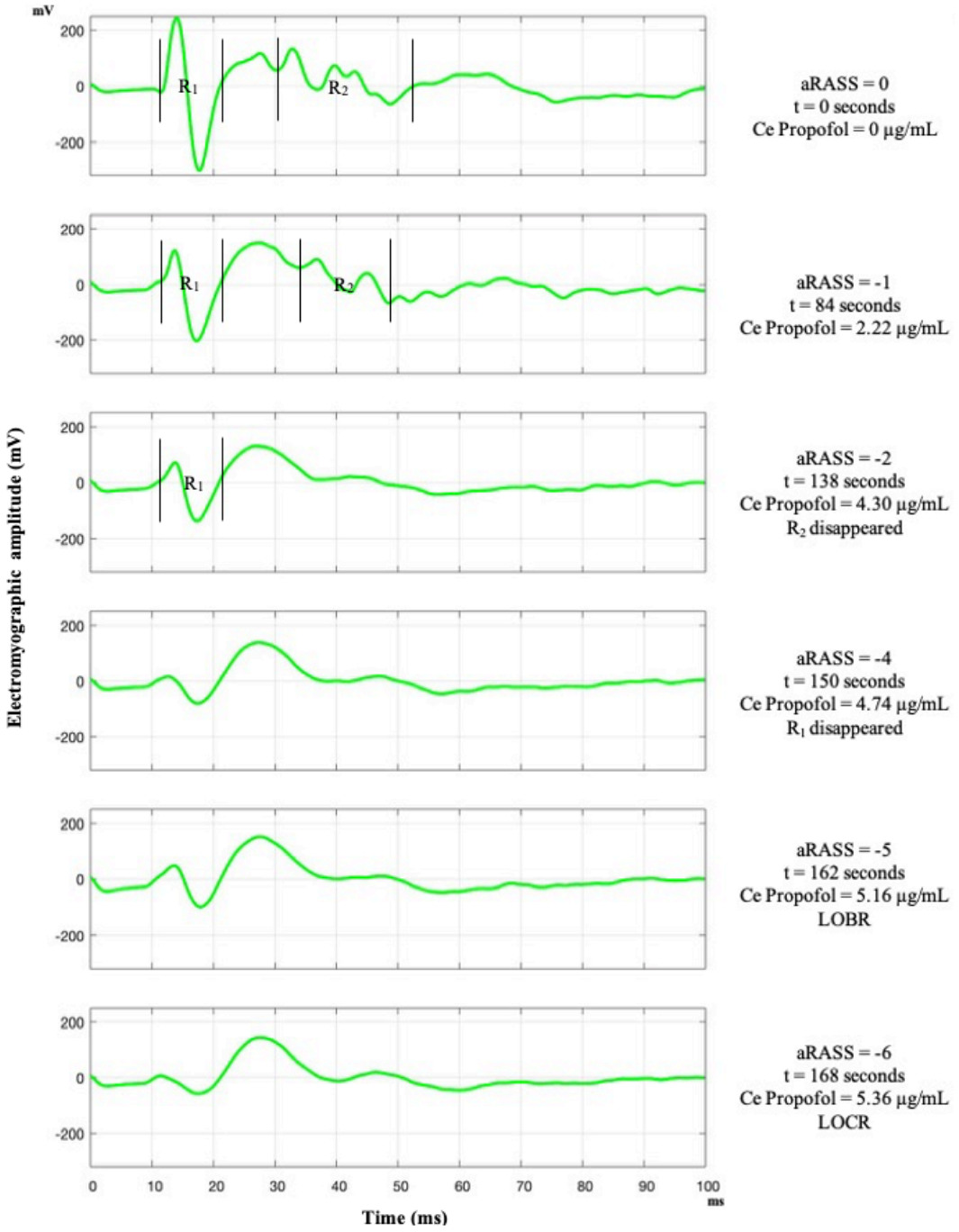


Figure 6.3 Example of electromyographic records of the average from four consecutive blink reflex responses of one patient. Each row shows the effects of the increasing administration of propofol. Amplitude and area of R_1 decreased with the depth of anesthesia. After 138 seconds of propofol infusion (t), the R_2 component disappears. R_1 component was last seen after 150 seconds. Loss of behavioral responsiveness (aRASS = -5) occurred after 162 seconds and loss of corneal reflex (aRASS = -6) occurred 168 seconds after propofol infusion, at an effect-site concentration of 5.36 µg/mL. Vertical lines mark the beginning and end of the individual components (R_1 and R_2), marked by an expert neurophysiologist at the end of the session, using the marker tool of the VikingQuest™ neurophysiological device.

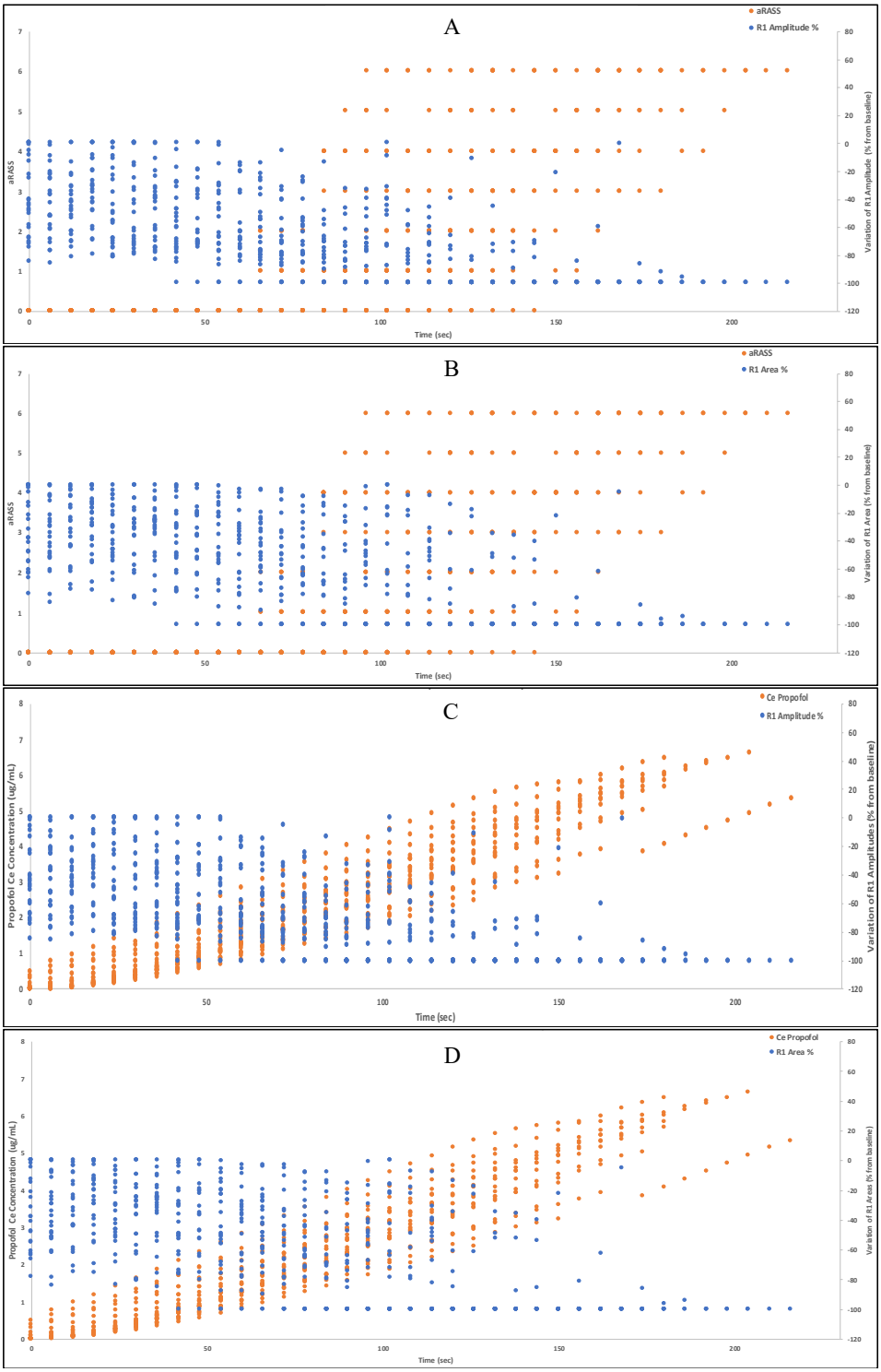


Figure 6.4 Values of variations from baseline areas and variations from baseline amplitudes of the first component of the blink reflex (R1) for all patients (n=25) are plotted against the adapted version of the Richmond Agitation-Sedation Scale (aRASS) (A-B) and the estimated effect-site (Ce) propofol concentration (C-D).

Table 6.2 Time since propofol started (seconds), predicted effect-site (Ce) concentrations of propofol (μg/mL), and adapted Richmond Agitation-Sedation Scale (aRASS) score at loss of R_2 (LOR_2), loss of R_1 (LOR_1), loss of behavioral response (LOBR) and loss of corneal reflex (LOCR) in all 25 patients. Results are mean ± standard deviation or median.

	Time since propofol started (seconds)	Predicted propofol Ce concentration (μg/mL)	aRASS score
LOR_2	49.68 ± 26.18	1.29 ± 0.82	-1
LOR_1	102.48 ± 33.00	3.04 ± 1.28	-2
LOBR	138.24 ± 28.49	4.22 ± 1.28	-5
LOCR	145.92 ± 28.45	4.50 ± 1.33	-6

The times for endpoints LOR_2, LOR_1, LOBR and LOCR were all statistically different from each other ($p<0.001$).

The relationship between the estimated propofol Ce concentration and LOR_2, LOR_1, LOBR and LOCR for all 25 patients, was characterized by the EC_{50} and the Hill's slope values (Table 6.3). Dose-response curves are presented in Table 6.5. EC_{50} of LOR_2 was found to be smallest, followed by the EC_{50} of LOR_1, LOBR and LOCR. The Hill's slopes of LOR_1 and LOR_2 were statistically significant ($p<0.001$), indicating a different variability between the concentrations of LOR_1 and LOR_2. The following Hill's slopes were not statistically different: LOR_1 versus LOBR ($p=0.2467$), LOR_1 versus LOCR ($p=0.2226$), and LOBR versus LOCR ($p=0.8976$).

Table 6.3 Predicted effect-site concentrations of propofol (μg mL^{-1}) that produces loss of R_2 (LOR_2), loss of R_1 (LOR_1), loss of behavioral response (LOBR) and loss of corneal reflex (LOCR) in 50% (EC_{50}) of patients.

	EC_{50}	(95% CI)	Hill's Slope	(95% CI)
LOR_2	1.249	(1.193, 1.304)	-2.475	(-2.791, -2.158)
LOR_1	3.025	(2.960, 3.090)	-4.368	(-4.882, -3.853)
LOBR	4.163	(4.092, 4.234)	-4.756	(-5.150, -4.362)
LOCR	4.470	(4.384, 4.555)	-4.795	(-5.234, -4.355)

Because R_2 responses were quickly abolished and, consequently, there were an insufficient number of data points, only R_1 responses are analyzed. Only the areas and amplitudes of R_1 were analyzed because, when a blink reflex component disappears, latency and duration cannot be measured, but areas and amplitudes are zero.

Table 6.4 shows that areas and amplitudes of R_1 component were correlated with aRASS, with amplitudes of R_1 correlating better than areas. Given this, Spearman's rho correlation coefficients were used to assess the relationship between the change in areas (and amplitudes) from the baseline to aRASS=-1 (i.e. when the patient is not fully alert, but has sustained awakenings to voice such as eye opening and eye contact) and the required dose of propofol to LOBR (and to LOCR). Results are presented in Table 6.5. There was a significant correlation between the change in amplitudes of the blink reflex component R_1 from baseline to aRASS=-1 and the concentration of propofol at LOBR (Rho=-0.445, p=0.026, N=25). Change in amplitudes from baseline to aRASS=-1 and the concentration of propofol at LOCR were also correlated (Rho=-0.424, p=0.035, N=25).

The association between aRASS and the estimated Ce concentration of propofol is given by P_k=0.593 (0.10) and by ρ=0.856 (0.060), showing a correlation, indicating that the clinical scale aRASS increased

monotonically and positively with increasing estimated propofol Ce concentrations until LOCR, revealing an increasing deepening of anesthesia.

There was no habituation of the R_1 component (habituation ≈ 2%). Difference between the first and fourth blinks of the R_1 component was not statistically significant (p=0.793). During the baseline recordings (0 mg propofol) and even after induction, R_2 showed a gradual decrease in area (habituation). The area of the fourth blink of R_2 was, on average, 22% lower than the first blink. Difference between the first and fourth blinks of the R_2 component were statistically significant (p<0.001).

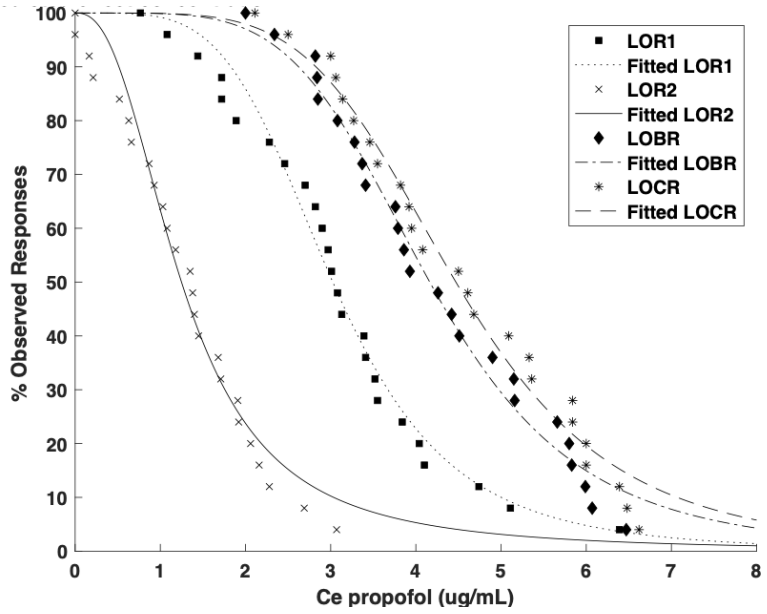


Figure 6.5 Propofol dose-response curve for loss of R_2 (LOR_2), loss of R_1 (LOR_1), loss of behavioral response (LOBR) and loss of corneal reflex (LOCR) regarding all patients. Filled squares and their corresponding best-fit dotted line denote LOR_1; crosses and their corresponding best-fit solid line denote LOR_2; filled diamond and their corresponding best-fit dashed-dot line denote LOBR and asterisks and their corresponding best-fit dashed line denote LOCR.

According to the presented clinical protocol for anesthesia, at LOCR, propofol infusion was stopped. However, following LOCR, predicted propofol Ce concentration continued to increase, resulting in a so-called overshoot. Since most individuals still had corneal reflex at LOR_1, it was investigated whether the increase of propofol concentration due to the overshoot if one would stop the infusion at LOR_1, would be enough for each individual to reach the required concentration of propofol to lose corneal reflex. Thus, a set of curves was simulated to compute the plasma and effect-site concentrations of propofol if one stops the propofol infusion at the time of LOR_1. Simulated curves ranged from the beginning of propofol infusion until 10 minutes after propofol was stopped, at LOR_1. The simulations were performed in Simulink/MATLAB, using the parameters of the Schnider pharmacokinetic model, as well as demographics, initial infusion rates and times of LOR_1. Figure 6.6 shows predicted and simulated plasma and effect-site concentrations (recorded by TCI system) of one patient, a female with 65 years old, 75 kg, 160 cm. Propofol infusion started at 220 mL/h and was kept for 168 s until LOCR, time at which propofol

infusion was stopped. At this point, although the plasma concentration begins to decrease, the propofol effect-site concentration continues to increase until a maximum point is reached. Plasma concentrations were used as references to find the stoppage time of the infusion. Estimated overshoot was then calculated, in μg/mL, as the difference between the maximum estimated effect-site concentration achieved after the propofol infusion was stopped and the estimated effect-site concentration at LOCR. Simulated overshoot was calculated, as the difference between the maximum simulated effect-site concentration achieved after the propofol infusion was stopped (if stopped at LOR_1) and the simulated effect-site concentration at LOR_1, in μg/mL. Estimated and simulated overshoots, in the example of were 0.57 μg/mL and 0.64 μg/mL, respectively.

Table 6.4 Correlations [mean prediction probability (group P_k) and mean Spearman's correlations (group ρ)] between the adapted Richmond Agitation-Sedation Scale (aRASS) score and the areas or amplitudes of blink reflex component R_1.

	aRASS				Propofol Ce Concentration			
	P_k	SD	ρ	SD	P_k	SD	ρ	SD
Area R_1	0.672	0.183	-0.688	0.165	0.739	0.107	-0.823	0.153
Amplitude R_1	0.709	0.134	-0.721	0.123	0.812	0.102	-0.838	0.113

Correlations were calculated for 25 patients individually and presented as the mean value for all patients and the standard deviation (SD)

For all 25 patients, the estimated overshoot was 0.62±0.31 μg/mL and the simulated overshoot was 0.71±0.13 μg/mL. The increase of propofol concentration due to the overshoot if one would stop the infusion at LOR_1 would not be enough to reach the effect-site concentration required to LOBR. The difference between the estimated propofol concentration at LOBR and LOR_1 was on average 4.22 – 3.04 = 1.18 μg/mL (Table 6.2).

Table 6.5 Spearman's correlations between the change in areas and amplitudes of the blink reflex component R_1 from baseline to adapted Richmond Agitation-Sedation Scale score -1 (aRASS=-1) and the effect-site (Ce) concentration of propofol at loss of behavioral response (LOBR) and loss of corneal reflex (LOCR) in all 25 patients.

		Propofol Ce Concentration at LOBR	Propofol Ce Concentration at LOCR
Change in Areas from baseline to aRASS=-1	*Correlation coefficient*	-0.314	-0.324
	Sig. (2-tailed)	0.127	0.114
	N	25	25
Change in Amplitudes from baseline to aRASS=-1	*Correlation coefficient*	-0.445*	-0.424*
	Sig. (2-tailed)	0.026	0.035
	N	25	25

*Correlation is significant at the 0.05 level (2-tailed).

Discussion

With this study, it was showed that neurophysiologically-derived parameters of EMG records of electrically evoked blink reflex could be used as surrogates of the Richmond Agitation-Sedation Scale to provide an objective endpoint of the cortical and brainstem effects of propofol in the continuum to unconsciousness.

The baseline blink reflex responses before propofol infusion in this study were similar to those found in the literature. Table 6.6 compares the values of measurements for the latency, area, duration, and amplitude of R_1 and R_2 in different studies.

After propofol infusion was started, there is a time when the second component of the blink reflex, R_2, was abolished and sometime later, the first component of the blink reflex, R_1, was also abolished. It was found that the R_2 component was last seen at an aRASS value of -1 and R_1 at an aRASS of -2. The differences in the degree of suppression of the two components of the reflex can be explained neurophysiologically. The R_1 component of the blink reflex is mediated predominantly by an oligosynaptic reflex arc which contains one or two interneurons [175]; however, the R_2 component is relayed through a polysynaptic path, including neurons in the reticular formation, where gamma aminobutyric acid (GABA) receptors are present [176], thereby representing the target for propofol [177]. Besides the GABA effect of propofol, it can also inhibit N-methyl-D-aspartate (NMDA) receptors, facilitating the inhibition of these reflex responses [178]. In addition, propofol depresses skeletal muscle excitability [179], thereby influencing the electromyographic response. The presence of remifentanil can also synergistically influence the effects of propofol [180].

The different sensitivity of the blink reflex components to propofol can be seen in Table 6.3 and Figure 6.5. The R_2 component was the most susceptible to the effects of propofol, while R_1 was the most resistant. Each blink reflex component and each endpoint studied (LOBR and LOCR) had a different EC_{50}. The EC_{50} of LOR_2 and LOR_1 are not coincident. The same happened to EC_{50} of LOR_1 and LOBR, with EC_{50} of LOR_1 and LOCR and with EC_{50} of LOBR and LOCR. Almost all patients lost the R_1 component when they still had clinically observed corneal reflex (24 patients). Only one patient lost R_1 at the same time as LOCR and two patients at the same time as LOBR.

Habituation, a gradual quantitative diminution of response to repeated uniform stimuli, is present in R_2 but not in R_1 during baseline recordings and even after induction of propofol. Habituation of R_2, although small in this study, is statistically significant. It can be prevented by using stimuli at a lower rate, but with the disadvantage of not providing the temporal discrimination usually used clinically in the center to determine LOBR.

Rapid abolition of the R_2 component due to its habituation resulted in an insufficient number of data points for us to analyze. The focus here was on the analysis of the R_1 component of the blink reflex for this reason. The R_1 component of the blink reflex has a strong correlation with aRASS scale. Amplitudes of R_1 correlated better with aRASS scale than areas. When the R_1 component of the blink reflex disappears, the latency cannot be measured, but area and amplitude are zero. This extra data point for the area and amplitude invariably resulted in a better correlation, because this zero area and amplitude coincided with a lower aRASS scale. The aRASS scale of the current study has a minor modification compared with the original RAAS scale, that is the adding of a corneal reflex endpoint because the loss of corneal reflexes is

a reliable indicator of impaired brainstem function due to the actions of the hypnotic agent on the nuclei in the pons and midbrain [181].

Another finding was that the R_1 component has a correlation with estimated propofol Ce concentrations and that aRASS scale was strongly correlated with estimated propofol Ce concentrations, indicating that the clinical scale aRASS increased monotonically and positively with increasing estimated propofol Ce concentrations until LOCR. This revealed an increasing deepening of anesthesia. Area and amplitude of the R_1 component showed to be good indicators to predict the different anesthetic levels (aRASS from 0 to -6) or to predict the estimated propofol Ce. Change in amplitude of the R_1 component from baseline to aRASS=-1 showed to be correlated with the propofol effect-site concentration required for both LOBR and LOCR. This may be an indication that it would be possible to estimate the individual need of propofol by knowing the amplitude response of the R_1 component right after the transition from the fully awake and alert state to the drowsy state. This could be a very interesting study in the field of modulation that would be performed in a near future.

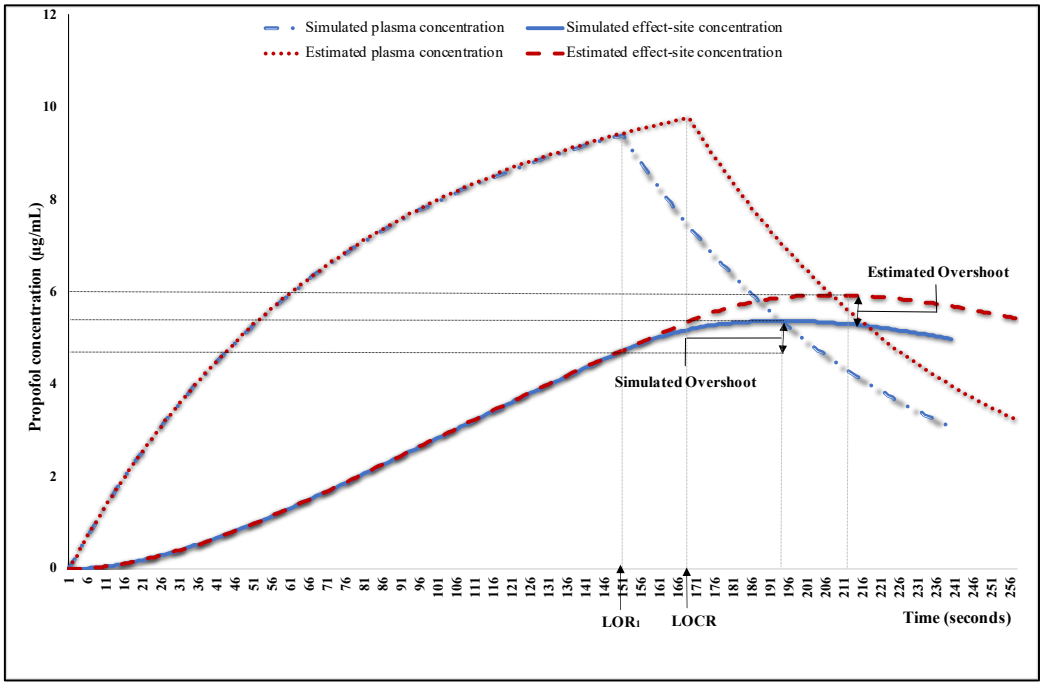


Figure 6.6 Effect-site and plasma concentrations of propofol during an intravenous administration with TCI system performed to one patient, female, 65 years old, 75 kg, 160 cm, with an infusion rate of 220 mL/h. Red lines represent the estimated concentrations of propofol, recorded by the TCI system (dashed line representing the effect-site concentrations and dotted line representing the plasma concentration). Blue lines represent the simulated concentrations of propofol, computed if propofol infusion stopped at LOR_1 (solid-line representing effect-site concentration and dash-dot-line representing plasma concentration). LOR_1 occurred 151 seconds after propofol started and corresponds to the peak maximum of the simulated plasma concentration. LOCR occurred 168 seconds after propofol started and corresponds to the peak maximum of the estimated effect-site concentration. Overshoot corresponds to the difference between the peak of the effect-site concentration and the effect-site concentrations at which the peak plasma concentrations was maximum.

To answer the question of whether neurophysiologic-derived parameters of EMG records of electrically evoked blink reflex are useful or not in identifying the moment of loss of responsiveness determined with a modified version of the RAAS scale in the continuum to unconsciousness, the answer is yes. Based on the findings, one can argue that due to overshooting, the proposed moment to stop the

propofol infusion would be after the patient loses the R_1 component of the blink reflex. This would then lead to a subsequent increase in the effect-site concentration from the already circulating plasma propofol and achieve a higher concentration that may be capable of abolishing the behavioral reflex, the target endpoint. If this subsequent increase was not enough, the infusion could be resumed for an increased dose [182].

The R_1 component of the blink reflex disappears before patients lose consciousness, i.e. LOCR>LOR_1. This differs from the results of Mourisse and colleagues [171], who have studied the relation between the clinical depth of sedation/anesthesia scale with the blink reflex, using a different sedation scale and a different anesthetic protocol. Mourisse's patients did not receive remifentanil, and propofol was administered in a stepwise deepening of anesthesia with different targets (calculated effect-site concentrations of 0 μg/mL, 0.5 μg/mL, 1 μg/mL, 1.5 μg/mL, 2.2 μg/mL, 3.5 μg/mL, 5.0 μg/mL, 6.0 μg/mL and 7.0 μg/mL) and only two minutes after reaching target effect-site concentrations, blink reflexes and depth of anesthesia scores were recorded. In this study, remifentanil infusion starts with an effect-site concentration target of 2.5 ng/mL and then patients received propofol by target-controlled infusion at an infusion rate of 3.3 $mL.kg^{-1}.h^{-1}$, in TCI-View mode, slowly and continuously, until LOBR. Probably due to the use of remifentanil, R_1 responses were abolished too soon. Although this study did not individualize the effects of propofol alone, which is a limitation of the actual study, it may be seen as offering the advantage of addressing the real scenario in which clinical anesthesia takes place every day. Another limitation of the presented approach is the use of estimated Ce concentration values in the absence of pseudo-equilibrium state, which may contribute to less accurate values. In contrast to Mourisse's study, the main goal of this study was to assess whether the blink reflex could be used as a clinical endpoint to identify loss of behavioral response. For this reason, the stimulations of the blink reflex were started before propofol infusion to establish a baseline. A slow infusion of propofol was then used to allow enough time to contemplate the transition from consciousness to unresponsiveness. The main goal was not to develop a new pharmacokinetic-pharmacodynamic model of propofol and blink reflex, but to investigate it in this transition period.

Nevertheless, the method of electromyographic recording of electrically evoked blink reflex in patients submitted to general anesthesia and in the continuum to unconsciousness, showed to be a possible method to continuously monitor the EMG, in awake, sedated or unconsciousness patients, during the onset to unconsciousness, and in a real scenario in which clinical anesthesia takes place every day. Patients also found the stimuli to be easily tolerable.

Based on these results, it is concluded that the blink reflex, although being an indicator of immobility, is not useful in precisely determining the absence of responsiveness. However, one can argue that there is an ideal concentration of propofol required to lose corneal reflex, which can be reached after the propofol infusion stops at LOR_1, due to overshooting. Future work would be developing a model capable of identifying this intermediate amount of propofol. It is also intended to perform an analysis of the EMG signals obtained from the blink reflex in the frequency domain to evaluate the capacity of several features, such as mean power, median frequency, and band-power, to predict the clinical aRASS scale and to predict the effect-site concentrations of propofol [183].

Table 6.6 Baseline blink reflex responses in the actual study and in other different studies.

	Reference	R_1	R_2
Latency (ms)	Actual study (N=25)	10.7 ± 0.9	38.2 ± 7.2
	Kimura [184] (N=83)	10.6 ± 0.8	31 ± 10.0
	Medvedeva [185] (N=31)	10.6 ± 0.9	33 ± 8.6
	Brooks [172] (N=400)	10.3 ± 0.9	32 ± 3.3
	Schwingenschuh [186] (N=9)	10.1 ± 0.7	34.6 ± 2.5
	Berardelli [187] (Below 50 years N=10)	11.9 ± 0.5	32.2 ± 2.6
	Berardelli [187] (Above 50 years N=10)	10.9 ± 1.4	32.5 ± 3.6
	Agostino [188] (N=11)	11.3 ± 0.9	33.1 ± 2.7
	Yoo [173] (N=54)	10.7 ± 0.6	31.17 ± 3.3
	Mourisse [189] (N=9)	10.0 ± 1.1	30.2 ± 4.2
	Mourisse [171] (N=20)	10.5 ± 1.0	31.9 ± 3.0
	Mourisse [174] (N=29)	12.3 ± 1.6	37.1 ± 3.8
Amplitude (μV)	Actual study (N=25)	405.4 ± 221.7	416.7 ± 193.6
	Berardelli [187] (Below 50 years N=10)	330.0 ± 90.7	340.0 ± 84.0
	Berardelli [187] (Above 50 years N=10)	230.0 ± 70.0	360.0 ± 78.3
	Kimura [184] (N=83)	380.0 ± 230.0	530.0 ± 240.0
	Medvedeva [185] (N=31)	256.3 ± 149.3	680.1 ± 253.3
	Agostino [188] (N=11)	216.0 ± 100.3	466.0 ± 159.0
	Yoo [173] (N=54)	164.7 ± 85.8	151.8 ± 59.8
Duration (ms)	Actual study (N=25)	9.2 ± 1.4	32.4 ± 10.1
	Medvedeva [185] (N=31)	-	31.0 ± 6.3
	Schwingenschuh [186] (N=9)	11.4 ± 2.9	49.1 ± 6.6
	Berardelli [187] (Below 50 years N=10)	-	71.0 ± 23.7
	Berardelli [187] (Above 50 years N=10)	-	82.5 ± 36.0
	Agostino [188] (N=11)	10.9 ± 2.4	38.2 ± 4.4
	Yoo [173] (N=54)	-	35.5 ± 5.4
	Mourisse [189] (N=9)	8.0 ± 2.8	45.1 ± 15.4
	Mourisse [171] (N=20)	11.0 ± 2.1	43.7 ± 9.8
Area	Actual study (N=25) (μV.ms)	1173.6 ± 505.8	2440.4 ± 1356.2
	Medvedeva [185] (N=31) (μV^2/ms)	-	22229.0 ± 10919.3
	Schwingenschuh [186] (N=9) (μVms)	490.0 ± 260.0	3300.0 ± 1600.0
	Mourisse [174] (N=29) (μVms)	1110.0	-

6.2 Performance of EMG-derived parameters from blink reflex: prediction probabilities and multinomial logistic analysis

Ana Leitão Ferreira MSc, Catarina S. Nunes PhD, Sérgio Vide MD, João Felgueiras MSc, Márcio Cardoso MD, Pedro Amorim MD, Joaquim Mendes PhD

Abstract

Introduction: The amount of propofol needed to induce loss of responsiveness (LORP) varied widely among patients, and they usually required less than the initial dose recommended by the drug package inserts. Identifying precisely the moment of LORP will determine the amount of propofol each patient needs. Currently, methods to decide the exact moment of LORP are based on subjective analysis, and the monitors that use objective methods fail in precision. Based on previous studies, it is believed that the blink reflex can be useful to characterize, more objectively, the transition from responsiveness to unresponsiveness. The purpose of this study is to investigate the relation between the electrically evoked blink reflex and the level of sedation/anesthesia measured with an adapted version of the Richmond Agitation-Sedation Scale (aRASS), during the induction phase of general anesthesia with propofol and remifentanil. Adding the blink reflex to other variables may allow a more objective assessment of the exact moment of LORP loss of responsiveness and a more personalized approach to anesthesia induction.
Results: The electromyographic-derived features proved to be good predictors to estimate the different levels of sedation/anesthesia. The results of the multinomial analysis showed a reasonable performance of the model, explaining almost 70% of the adapted Richmond Agitation-Sedation Scale aRASS variance. The overall predictive accuracy for the model was 73.6%, suggesting that it is useful to predict LORP.
Conclusions: The developed model was based on the information of the electromyographic-derived features from the blink reflex responses. It was able to predict the drug effect in patients undergoing general anesthesia, which can be helpful for the anesthesiologists to reduce the overwhelming variability observed between patients and avoid many cases of overdosing and associated risks. Despite this, future research is needed to account for variabilities in the clinical response of the patients and with the interactions between propofol and remifentanil. Nevertheless, a method that could allow for an automatic prediction/detection of LORP is a step forward for personalized medicine.

Keywords: Blink Reflex, Loss of Responsiveness, Anesthesia Monitoring, Prediction, Propofol, Sedation.

Introduction

In clinical practice, anesthesiologists use a variety of anesthetic drugs during surgery to render the patient unconscious/unresponsive, including the most widely used, intravenous drug propofol. In a previously published work [107][20], it was found that the amount of propofol needed to induce loss of responsiveness (LORP) varied widely among patients (~300%) and that more than two-thirds of the patients required less than the initial dose recommended by the drug package inserts.

Identifying precisely the moment of LORP during the induction phase of general anesthesia is of extreme importance for the determination of the amount of propofol each patient needs. Using that information will help to guide the drug infusion rate required to maintain an adequate level of anesthesia throughout the surgery [190][191][192].

Currently, methods to decide the exact moment of LORP are based on subjective analysis [193]. Objectively, there are depth of anesthesia monitors, such as the Bispectral Index (BIS) (Aspect Medical System, Newton, MA, USA), which allow the maintenance of a steady-state during surgery, but do not enable the determination of the instant at LORP, which remains an open issue. BIS evaluation is characterized by a delay following the acquisition of a new dataset, which may even exceed one minute [140]. To prevent complications, such as awareness [11][21] or excessive anesthesia, the anesthesiologists should be aware of the conditions that cause incorrect BIS readings.

In a previous study, Mourisse et al. [171] found that the components of the blink reflex are attenuated and abolished with increasing concentrations of propofol. Mourisse et al. [174] showed, in another study that the blink reflex was more sensitive than BIS. Their results suggested that the differential sensitivity of the blink reflex components could be useful to monitor the depth of sedation/anesthesia, and thus, to detect when LORP occurs. However, their method used a ten-minute stepwise increment in propofol, which is not compatible with anesthesia induction in a surgical setup.

It is hypothesized that the blink reflex can be useful to characterize, more objectively, the transition from responsiveness to unresponsiveness during the induction of anesthesia with propofol and remifentanil. The administration of propofol may be stopped at this transition, personalizing the amount of propofol each patient requires and reducing the events of over and underdosing. Then, this can be used to titrate the infusion rate of propofol and to maintain an adequate level of sedation/anesthesia. In the current study and based on a constant infusion of propofol at a slow rate, it is intended to investigate the relationship between the electrically evoked blink reflex and the level of sedation/anesthesia. For this purpose, different electromyogram (EMG) features were extracted, and the ability of these features to distinguish between different levels of sedation/anesthesia was compared. The comparison was carried out using prediction probability analysis and multinomial logistic modeling. Adding the blink reflex to other variables already recorded during general anesthesia may allow a more objective assessment of the exact moment of LORP and a more personalized approach to anesthesia induction.

Methods

Patients

Twenty-five patients aged over 18 years (ASA I, II or III), scheduled for neurosurgical procedures participated in this study. They had no hemodynamic, respiratory or ophthalmic problems, and did not use

analgesics, psychotropic or excessive alcohol consumptions. The Hospital Ethical Committee approved the study and all subjects gave informed written consent. No premedication was given. The study took place in a quiet, warm anesthetic induction room. Before the start of the study, the patients were prepared as usual for anesthesia (intravenous access, continuous electrocardiogram, pulse oximetry, and non-invasive blood pressure).

Anesthetic protocol

The standard practice for neurosurgical procedures consists of opioid-propofol anesthesia using a Target Controlled Infusion (TCI) system. In the operating room, after placement of standard monitor and an intravenous line in the dorsum of the hand, an infusion of a balanced electrolytic solution was started at 6 $mL.kg^{-1}.h^{-1}$. The anesthesiologist would then use a Fresenius Base Primea docking station (Fresenius-Kabi, Bad Homburg, Germany) to start a TCI of remifentanil (Minto PK-PD model) [12][13], at an effect-site concentration (Ce) target of 2.5 $ng.mL^{-1}$. A bolus of 10 mg of lidocaine was administered locally to reduce the pain associated with propofol administration. One minute after the remifentanil pseudo-equilibration was achieved, baseline blinks were recorded and, then, an infusion of 1% propofol (Schnider PKPD model) [14] was started using a TCI enabled infusion system, in the TCI-View mode, at 3.3 $mL.kg^{-1}.h^{-1}$ until LORP, determined by the anesthesiologist. This slow velocity of infusion during induction enabled a careful titration of the minimum amount of propofol required for loss of responsiveness. Once LORP was reached, the propofol infusion was stopped, the estimated propofol Ce concentration was noted and the TCI system was switched to effect-site TCI mode with a Ce of 75% of that at LORP. At this point, no additional analgesic/opioid medication was given during induction. Propofol infusion was subsequently titrated to maintain BIS (BIS Vista™ monitor – Medtronic, Ireland) between 40 and 60. The study was terminated just before tracheal intubation.

Data Acquisition

Using the VikingQuest™ neurophysiological system (VikingQuest, Nicolet, WI, USA) the electromyographic stimulations and recordings were performed at a total sweep time of 200 ms with a sample rate of 10kHz. A high-pass filter was applied with a cutoff frequency of 20 Hz. Before the induction of anesthesia and prior electrode application, all the patient's head skin surfaces were cleaned with an exfoliant agent. Surface electrodes (1.4 cm^2) coated with alcohol and conductive paste (electrode impedance < 8 kΩ) were applied to stimulate and record the electromyogram from the right orbicularis oculi muscle. The right supraorbital nerve was transcutaneously stimulated using a bipolar electrode with the cathode placed beneath the eyebrow over the supraorbital notch and the anode placed above the eyebrow (interelectrode distance 2 cm). The supraorbital nerve was electrically stimulated with a duration of 0.1 ms at 0.16 Hz. With regard to the electrode, the recording electrode was placed in the middle of the inferior rim of the orbit; the reference halfway on the eye-ear line and the ground electrode was placed on the cheek or on the shoulder of the patient (Figure 6.7). The signals were stored in the VikingQuest™ software provided by the manufacturer. The raw data was exported to a personal computer to be treated and analyzed in MATLAB® 2019b (MathWorks, USA).

Assessment of levels of responsiveness

The level of sedation was assessed every six seconds using an adapted version of the Richmond Agitation-Sedation Scale (RASS) score [144], entitled aRASS. This scale is a modification of the RASS scale [144], with the addition of the corneal reflex endpoint, yielding an adapted Richmond Agitation-Sedation Scale (aRASS). A score of 0 corresponds to a fully awake and alert behavior, -1 with a not fully alert behavior, but a sustained awakening to voice (eye-opening and eye contact), -2 with a brief awakening to voice (eye-opening and eye contact, -3 no response to voice, but movement or eye-opening to shaking and shouting, -4 is no response after shaking and shouting, but still have the corneal reflex and -5 is no corneal reflex. Loss of responsiveness (LORP), defined as -5 in aRASS scale was evaluated using a drop of sterile water to the cornea, after aRASS reached a score of -4. Hereafter, this evaluation was intercalated with electrical stimulations at 6 seconds intervals. If the eyes blinked concomitantly, the reflex was intact. If only one eye blinked, the reflex was impaired, and if neither eye blinked, the reflex was absent.

Baseline blink reflexes and evaluation of the aRASS scale were recorded several times before propofol was administered. Patients then received propofol, and at the same time four successive blink reflexes were elicited and recorded. A further four successive blink reflex stimuli were elicited after a 6-second interval and recorded continuously until LORP was reached.

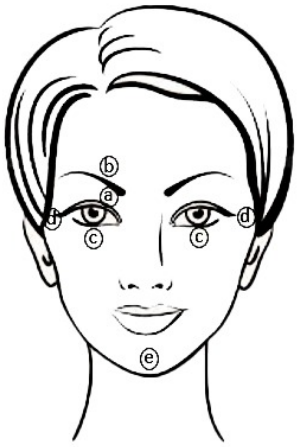


Figure 6.7 Electrode placement for blink reflex monitoring. Electrodes a (cathode) and b (anode) are electrodes used for electrical stimulation. Electrodes c (active) and d (reference) are silver disc recording electrodes. Electrode e is a ground electrode.

Blink reflex parameters

The blink reflex neurophysiology and anatomy are reasonably well known [194]. The electromyography records of an electrically evoked blink reflex showed at least two components (R_1 and R_2 components). The first or early response (R_1) is brief and occurs after a latency of approximately 10 ms on the side of stimulation [168]. The second response (R_2) has a latency of approximately 30 ms, is bilateral, and more prolonged in time [168]. The R_2 response causes the actual contraction of the orbicularis oculi muscle [168]. The optimal stimulus intensity was sought by gradually increasing the current until visual observation of the EMG showed that, in the presence of a visible R_1 component, the R_2 component reach its maximum amplitude [169].

Figure 6.8, uppermost panels, illustrates the two components of a normal blink reflex. The averaged electromyographic records of the blink reflex were obtained from the four consecutive electrical stimulation of the supraorbital nerve (interstimulus interval 5 ms). The first rows showed baselines. Vertical lines marked the beginning and end of the individual components (R_1 and R_2), marked by an expert neurophysiologist at the end of the session, using the marker tool of the VikingQuest™ neurophysiological device. The right margins showed estimated propofol concentrations (µg/mL), clinical endpoints (loss of R_1, loss of R_2 and LORP), depth of sedation/anesthesia level (aRASS score), and the time since propofol started.

Data Analysis

Before proceeding with data analysis, the DC component was removed by subtracting the mean amplitude from the EMG signals. The best straight-fit line (in the least-squares sense) was then removed from the EMG signals with the detrend function of MATLAB®.

For each pre-processed EMG signal, two specific subsets of samples were selected: T_1, from 10 ms to 25 ms, in which it is expected R_1 to be analyzed, and T_2, from 25 ms to 200 ms, in which R_2 is expected to be analyzed.

Data from each subset was analyzed in both time and frequency domain. In the time domain, after rectifying and normalizing each subset of data, the following features were extracted: mean amplitude (V_{mean}), and the difference between the maximum (equal to 1) and the mean amplitudes (V_{diff}).

Because R_2 and R_1 responses were abolished before LORP and, consequently, there was an insufficient number of data points, a frequency domain analysis was also performed. A non-parametric Fast Fourier Transform (FFT) using Welch's modified periodogram was used to extract functions from the frequency domain. EMG was windowed with a Hamming window and the modified periodogram was calculated for each time period. The Power Spectrum Density (PSD) was estimated by averaging over all resulting periodograms. For this purpose, MATLAB® was used. The following features from the frequency domain were extracted:

- Mean power (P_{mean} [dB]): The arithmetic mean value of the PSD estimate;
- Maximum power (P_{max} [dB]): The maximum value of the PSD estimate;
- Mean frequency (f_{mean} [Hz]): The average frequency which is calculated as the sum of product of the power spectrum of the PSD estimate and the frequency divided by the total sum of the power spectrum [195].
- Power at f_{mean} ($P_{meanfreq}$ [dB]): The value of the PSD estimate corresponding to the f_{mean}.
- Median frequency (f_{median} [Hz]): The frequency at which the power spectrum of the PSD estimate is divided into two regions with equal areas;
- Band power (P_{band} [dB]): The sum of the PSD estimate values within the frequency range 30-120 Hz;
- Total power (P_{total} [dB]): The sum of all the PSD estimate values;
- Ratio between P_{total} and f_{median} (P_{total}/f_{median} [dB/Hz]);
- Signal-to-noise ratio (SNR [dB]): The ratio of the PSD of the signal (meaningful information) with respect to the power of the background noise;

- Power bandwidth ($P_{bandwidth}$ [dB]): The 3-dB (half-power) bandwidth of the PSD estimate;
- Spectral entropy: The Shannon Entropy of the PSD estimate, i.e. the evaluation of the shape of the PSD estimate [196].

A. Prediction Probability Analysis

The capacity of the extracted features to detect the different sedation/anesthetic levels reflected in the numerical scale of anesthesia, aRASS was evaluated using prediction probability (P_k) statistics by correlating the parameter values during the two different study periods with the numerical scale.

To calculate P_k, a user-friendly program was used, the Pk Tool version 3.0, which included a context help. and colleagues [197] kindly provided the software and developed the algorithm according to the original[198].A value of P_k =0.5 means that the indicator/feature correctly predicts the sedation/anesthetic states only 50% of the time, i.e., no better than a 50:50 chance. A value of P_k =1 means that the indicator/feature predicts the aRASS correctly 100% of the time. P_k was calculated using pooled data from all patients.

B. Multinomial Logistic Analysis

The relation between the aRASS level of sedation/anesthesia and the EMG effect reflected in each extracted feature was modeled with a multinomial logistic regression (MLR) using a multiple predictor features defined by:

$$ln\frac{P}{1-P} = \beta_0 + \sum_{k=1}^{n} \beta_k X_k \quad (2)$$

Where *P* represents an outcome (or dependent variable) as a probability, $\beta_0 \ldots \beta_n$ represent the constant of the coefficients of the regression model, and $X_1 \ldots X_n$ represent the predictor (or independent) variables [199].

Statistics

The Kolmogorov-Smirnov test was used to test for normal distribution. Paired Samples t-test or Wilcoxon signed-rank test was used to compare the means of related data. Correlation analysis was performed using the Pearson R test for normally distributed data or the Spearman rank R when data were not normally distributed. Data were presented as Mean along with Standard Deviation (SD) and 95% confidence interval (CI), unless stated otherwise, in the logistic regression analysis.

In the same experimental session of each subject, the regression models were evaluated using mean values, otherwise, the variance of each predictor variable would be computed as much lower. *P*-value < 0.05 was considered to be statistically significant.

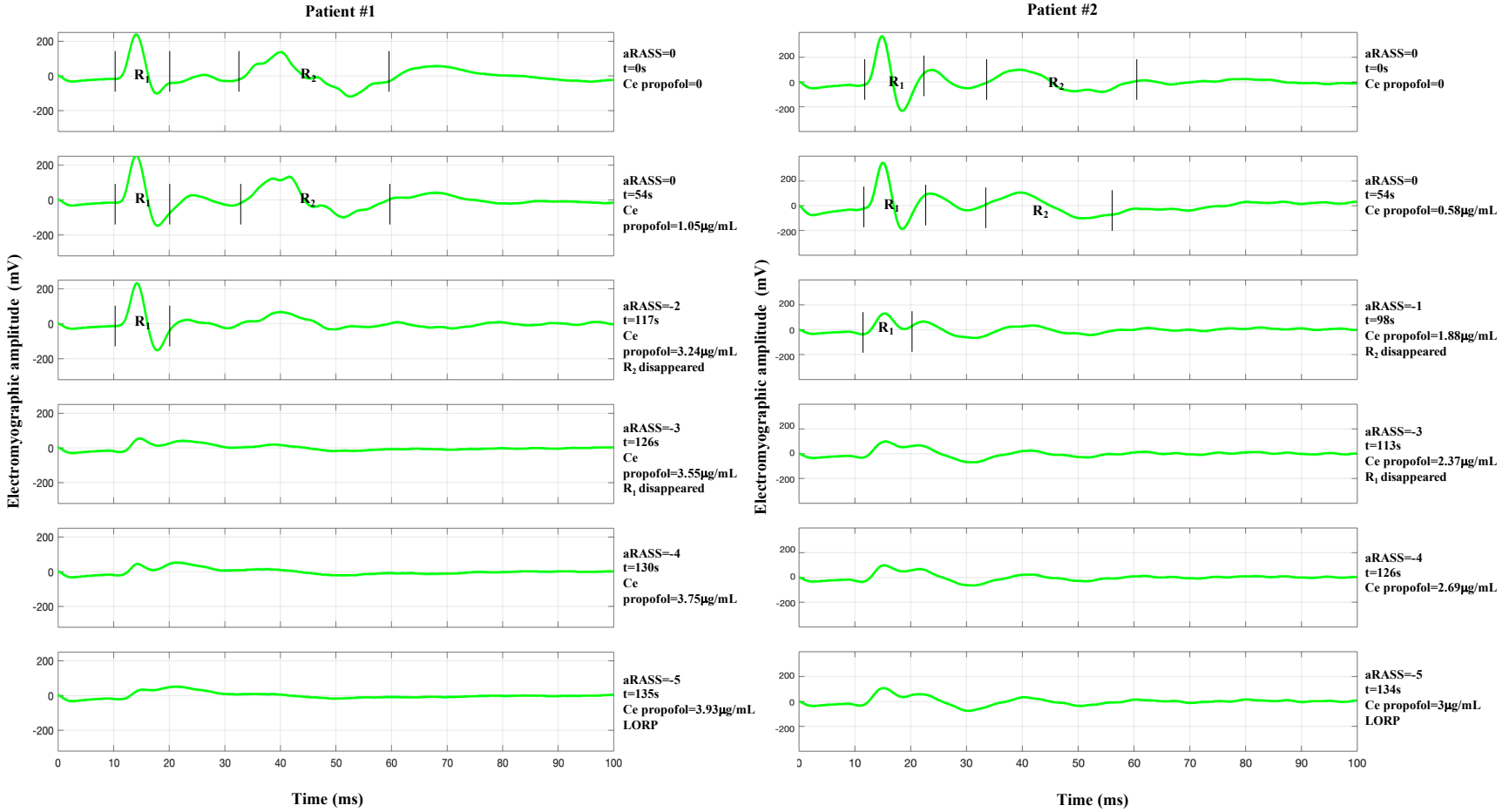


Figure 6.8 Examples of electromyographic records of the average from four consecutive blink reflex responses of a) Patient #1: a male patient (60 years, 65 kg), and b) Patient #2: a female patient (47 years, 64 kg) who participated in this study. Each row shows the effects of the increasing administration of propofol. In Patient #1, after 117 seconds of propofol infusion, the R_2 component disappeared. R_1 component was last seen after 126 seconds, loss of responsiveness (aRASS=-5) occurred after 135 seconds after propofol infusion, at an effect-site concentration of 3.93 µ/mL. In Patient #2, after 98 seconds of propofol infusion, the R_2 component disappeared. R_1 component was last seen after 113 seconds, loss of responsiveness (aRASS=-5) occurred after 134 seconds after propofol infusion, at an effect-site concentration of 3.00 µ/mL.

Results

Twenty-five patients (16 female and 9 male), aged 61 ±13, weighing 72 ± 11 kg, heighten 162 ± 9 cm, 1 ASA I, 18 ASA II, 6 ASA III were enrolled. The supraorbital nerve was stimulated with 25.7 ± 8 mA. All patients reached the end of the depth of sedation/anesthesia scale. No patient had hemodynamic or respiratory problems.

Visual inspection of the raw electromyogram and analysis of the signal quality was performed before extracting the features to eventually discard poor quality electromyogram. No signal was discarded.

Raw data from the study are presented in Figure 6.9; each patient's observed aRASS scores are plotted against the corresponding predicted propofol effect-site concentrations.

Concerning the raw electromyographic findings, after the propofol infusion was started, R_1 and R_2 decreased gradually. Ce concentrations, aRASS values, and times at which LOR_2, LOR_1 and LORP occurred are presented in Table 6.7. R_2 was the first component to be abolished, followed by the R_1 component. aRASS median [minimum, maximum] for LOR_2 was 0 [0, -2] and for LOR_1 was -2 [0, -4]. All patients were responsive (aRASS < -5) when the R_2 and R_1 responses were last seen.

There was a statistically significant difference between the propofol Ce concentration at LORP and LOR_1 ($p<0.05$). The times for endpoints LOR_2, LOR_1 and LORP are all statistically different from each other ($p<0.001$).

The time between LORP and LOR_1 was 35.68 ± 23.41 seconds. The amount of propofol given between LOR_1 and LORP was 1.23 ± 0.82 μg/mL.

Results of the features extracted from the EMG signals in the time and frequency domain are presented in Table 6.8.

Prediction Probability and Spearman Correlation Coefficient

The capacity of all extracted features to adequately assess the clinical sedation/anesthetic depth was evaluated by P_k analyses. The user interface is shown in Figure 6.10. The calculated P_k values and correlation coefficients of the EMG extracted features are shown in Table 6.9. P_k values were higher ($P_k>0.700$) in the period T_1 for V_{mean}, V_{diff}, f_{mean}, f_{median}, $P_{bandwith}$, and spectral entropy; and in the period T_2 for f_{mean}, and spectral entropy. Results indicated that during the period T_1 there was a significant negative association, defined by a correlation coefficient R higher than -0.500 and a $p<0.05$, between aRASS and f_{mean}, f_{median}, and spectral entropy. During the period T_1 there was a significant negative association between propofol Ce concentration and the following features: f_{mean}, f_{median}, and spectral entropy. There was no significant correlation between aRASS and the extracted features, and no significant association between the Ce concentration of propofol and the extracted features.

The correlation between aRASS and the propofol Ce concentration was given by $P_k=0.886$, SE=0.007 and by R=0.751, $p<0.01$. The clinical scale of the depth of sedation/anesthesia increased monotonically and positively with increasing propofol Ce concentration until LORP, revealing an increasing deepening of sedation/anesthesia.

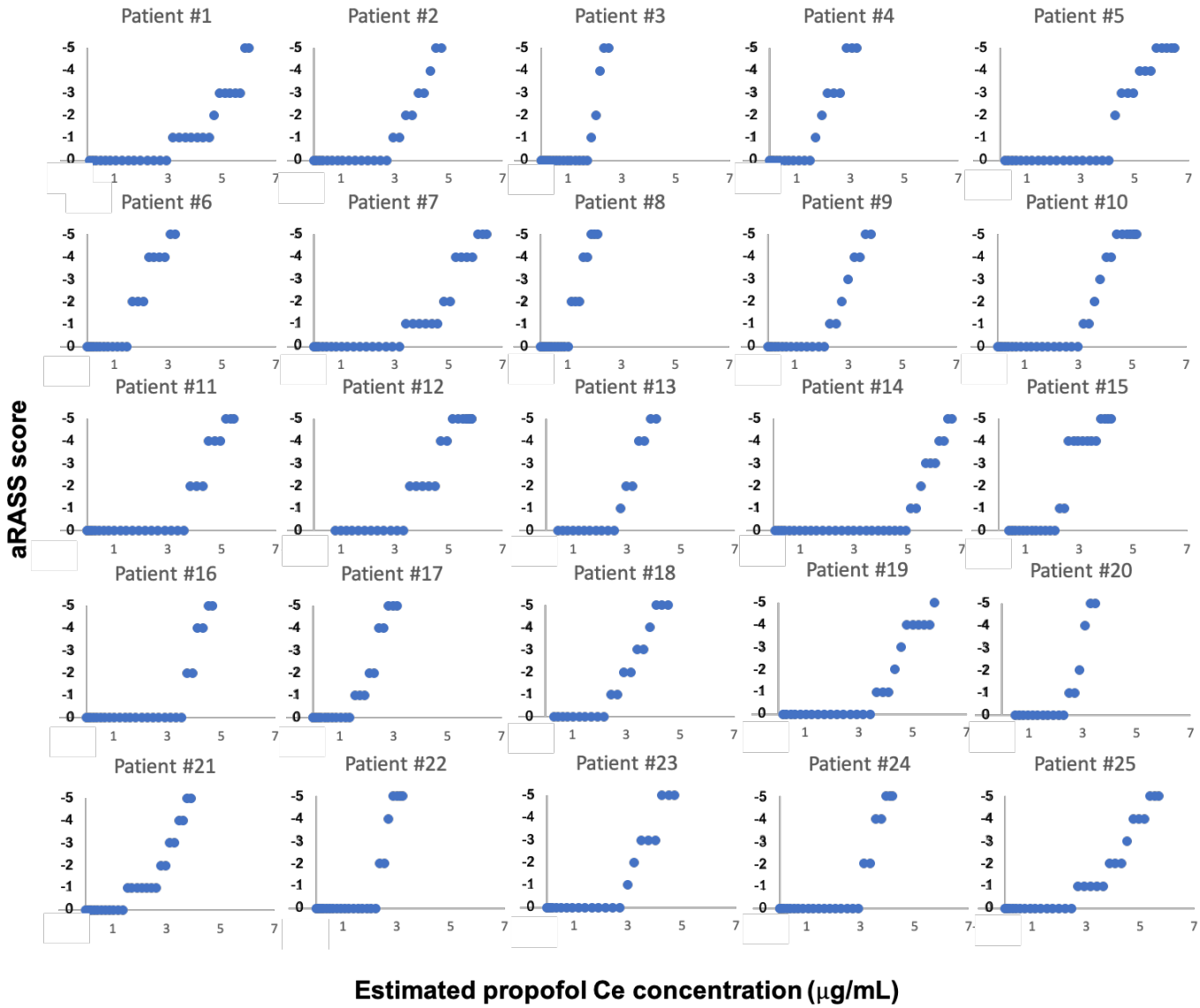


Figure 6.9 The predicted propofol effect-site concentration vs adapted Richmond Agitation-Sedation Scale (aRASS).

Table 6.7 Estimated effect-site concentration of propofol, adapted Richmond Agitation-Sedation Scale values, and times at which LOR_2, LOR_1 and LORP occurred. Results are mean ± standard deviation or median [minimum, maximum].

	LOR_2	LOR_1	LORP
Time since propofol started (s)	64.70 ± 23.72	112.16 ± 30.82	147.84 ± 27.36
Estimated propofol Ce concentration (μg/mL)	1.45 ± 0.85	2.99 ± 1.19	4.22 ± 1.24
aRASS score	0 [0, -2]	-2 [0, -4]	-5

LOR_2=Loss of R_2 component; LOR_1=Loss of R_1 component; LORP=Loss of responsiveness; aRASS=adapted Richmond Agitation-Sedation Scale; Ce=Effect-site concentration.

Multinomial Logistic Analysis

Regarding MLR, the features which were better correlated with the Ce concentration of propofol and with aRASS were chosen, and features which it was believed were useful (with a P_k>0.700). The predictor features corresponding to these criteria were propofol Ce, and V_{mean}, V_{diff}, f_{mean}, f_{median}, $P_{bandwith}$ and spectral entropy, during the period T_1, and f_{mean} and spectral entropy during the period T_2.

The effects of these variables were explored by building the MLR model and then examining the results. To achieve this goal, SPSS software version 26 was used, and the MLR model with response variable and all explanatory variables to make the primary model was calculated.

The overall effectiveness of the model was assessed using Chi-squared statistics. The Chi-square value of 696.430 and its respective p-value<0.001 indicated a significant relationship between the depth of sedation/anesthesia scale and the set of features in the final model. Model performance (Nagelkerke R^2) of the MLR for the combined features predicting aRASS level of sedation/anesthesia groups was 0.697. The overall predictive accuracy for the present model was 73.6%.

The likelihood ratio test shows the contribution of each feature to the model (Table 6.10).

Propofol Ce, f_{mean} (T_1), spectral entropy (T_1), and spectral entropy (T_2) had a significant contribution ($p<0.05$) to the model that predicts the aRASS's level of sedation/anesthesia, but not V_{mean} (T_1), f_{median} (T_1), $P_{bandwidth}$ (T_1) or f_{mean} (T_2). Figure 6.11 illustrates the relation between the aRASS score and the mean of the significant aforementioned features.

The fitted logistic model was

$$\ln\left(\frac{P}{1-P}\right) = -339.206 + 2.476 \times \text{Propofol Ce} - 0.281 \times V_{mean}(T_1) - 5.422 \times f_{mean}(T_1) + 3.234 \times f_{median}(T_1) + 0.116 \times P_{bandwith}(T_1) + 1441.537 \times \text{Spectral entropy } (T_1) + 0.074 \times f_{mean}(T_2) - 38.100 \times \text{Spectral entropy } (T_2) \quad (3)$$

Where *P* is the estimated probability of unresponsiveness (i.e. aRASS = -5).

Discussion

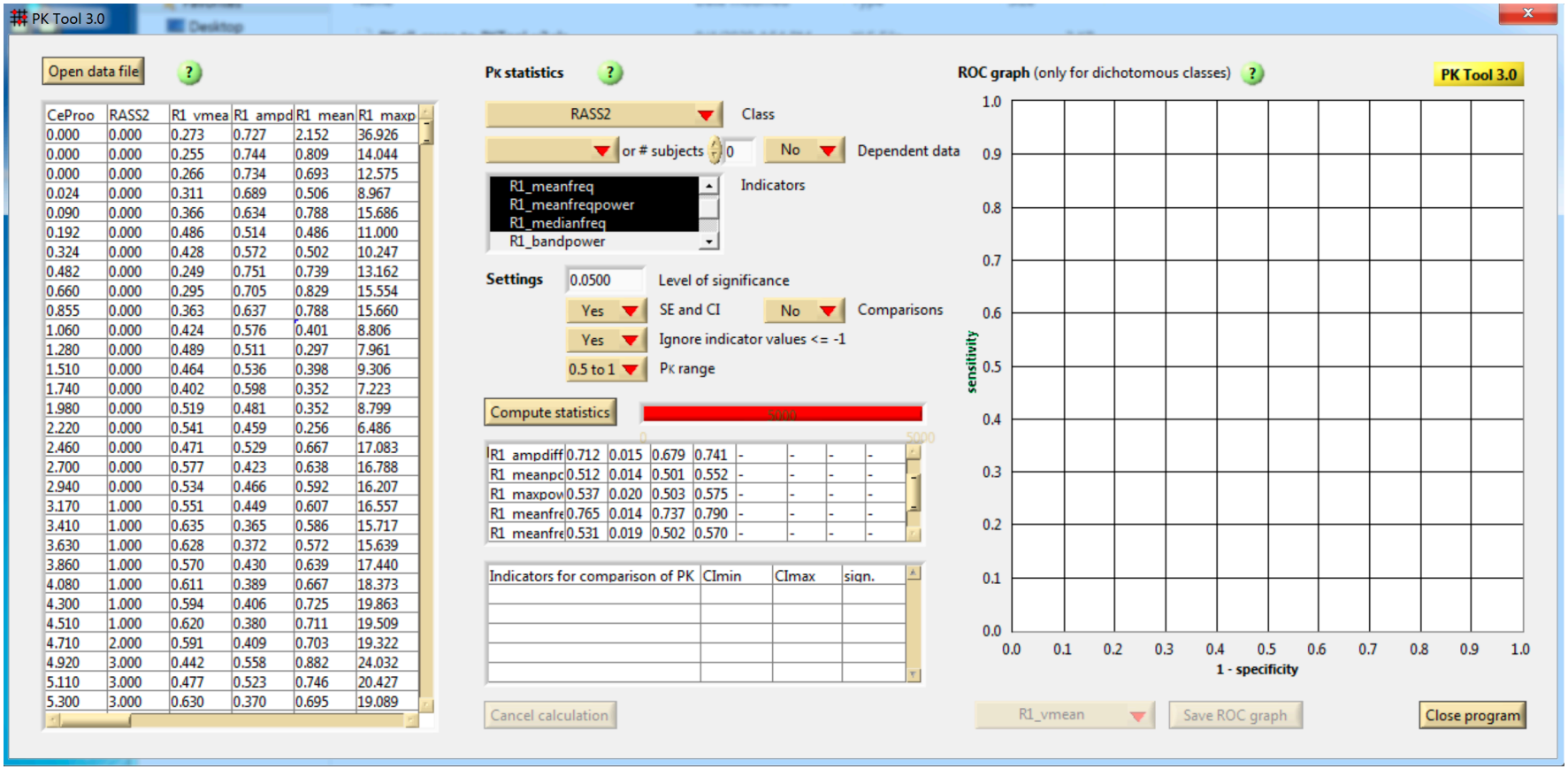
In the present study, a standard electrical stimulus to evoke a blink reflex was used during the induction phase of general anesthesia with propofol and remifentanil to assess the relation between the recorded electromyogram and the level of sedation/anesthesia. The level of sedation was assessed every six seconds using an adapted version of the Richmond Agitation-Sedation Scale, entitled aRASS.

The electromyographic-derived features were extracted during two specific subsets of samples: T_1, from 10 ms to 25 ms, in which it was expected the first response of the blink reflex, R_1, to be analyzed, and T_2, from 25 ms to 200 ms, in which the second response of the blink reflex, R_2, was expected to be analyzed.

Table 6.8: Values from the extracted features during two different time windows: P_1- from 10 ms to 25 ms, in which it is expected R_1 to be analyzed; P_2 – from 25 ms to 200 ms, in which R_2 is expected to be analyzed.

Parameter		Minimum	Maximum	Mean	Standard Deviation	Median
P_1	V_{mean}	0.190	0.721	0.443	0.126	0.445
	V_{diff}	0.280	0.840	0.556	0.126	0.555
	P_{mean} (dB)	0.166	15.162	2.660	2.879	1.555
	P_{max} (V)	3.770	436.561	68.613	78.169	37.462
	f_{mean} (Hz)	103.648	203.160	123.763	18.525	116.347
	P_{fmean} (V)	2.793	314.897	50.984	57.029	28.624
	f_{median} (Hz)	89.179	168.352	105.909	16.692	98.161
	P_{band} (dB)	596.219	62514.798	10151.828	11349.090	5730.088
	P_{total} (dB)	836.969	76399.833	13403.153	14506.321	7834.622
	P_{total}/f_{mean}	7.190	845.757	132.339	151.067	71.768
	SNR	-11.314	34.838	-6.980	2.886	-7.847
	$P_{banwidth}$ (dB)	157.941	310.036	188.047	33.105	172.167
	Spectral entropy	0.412	0.546	0.445	0.026	0.436
P_2	V_{mean}	0.130	0.575	0.320	0.088	0.310
	V_{diff}	0.425	0.870	0.680	0.088	0.690
	P_{mean} (dB)	0.007	14.787	0.509	1.035	0.184
	P_{max} (V)	0.363	868.099	24.534	52.506	9.724
	f_{mean} (Hz)	23.459	181.467	58.488	30.876	48.865
	P_{fmean} (V)	0.169	868.099	21.972	50.663	8.263
	f_{median} (Hz)	22.419	167.057	46.844	26.412	38.396
	P_{band} (dB)	32.975	73225.083	2337.29	4792.514	875.481
	P_{total} (dB)	35.038	74511.906	25660.961	5216.244	926.853
	P_{total}/f_{mean}	0.859	2736.873	63.886	156.724	23.885
	SNR	-8.038	44.143	8.691	11.550	4.456
	$P_{banwidth}$ (dB)	37.304	250.824	66.134	33.175	53.062
	Spectral entropy	0.180	0.496	0.299	0.072	0.278

V_{mean}=mean amplitude; V_{diff}=difference between maximum and mean amplitude; P_{mean}=mean power; P_{max}=maximum power; f_{mean}=mean frequency; $P_{meanfrequency}$=power at mean frequency; f_{median}=median frequency; P_{band}=power band; P_{total}=total integrated of the spectrum; P_{total}/f_{median}=ratio between total power and median frequency; SNR=signal-to-noise ratio and $P_{bandwidth}$=power bandwidth.



CeProo	RASS2	R1_vmea	R1_ampd	R1_mean	R1_maxp
0.000	0.000	0.273	0.727	2.152	36.926
0.000	0.000	0.255	0.744	0.809	14.044
0.000	0.000	0.266	0.734	0.693	12.575
0.024	0.000	0.311	0.689	0.506	8.967
0.090	0.000	0.366	0.634	0.788	15.686
0.192	0.000	0.486	0.514	0.486	11.000
0.324	0.000	0.428	0.572	0.502	10.247
0.482	0.000	0.249	0.751	0.739	13.162
0.660	0.000	0.295	0.705	0.829	15.554
0.855	0.000	0.363	0.637	0.788	15.660
1.060	0.000	0.424	0.576	0.401	8.806
1.280	0.000	0.489	0.511	0.297	7.961
1.510	0.000	0.464	0.536	0.398	9.306
1.740	0.000	0.402	0.598	0.352	7.223
1.980	0.000	0.519	0.481	0.352	8.799
2.220	0.000	0.541	0.459	0.256	6.486
2.460	0.000	0.471	0.529	0.667	17.083
2.700	0.000	0.577	0.423	0.638	16.788
2.940	0.000	0.534	0.466	0.592	16.207
3.170	1.000	0.551	0.449	0.607	16.557
3.410	1.000	0.635	0.365	0.586	15.717
3.630	1.000	0.628	0.372	0.572	15.639
3.860	1.000	0.570	0.430	0.639	17.440
4.080	1.000	0.611	0.389	0.667	18.373
4.300	1.000	0.594	0.406	0.725	19.863
4.510	1.000	0.620	0.380	0.711	19.509
4.710	2.000	0.591	0.409	0.703	19.322
4.920	3.000	0.442	0.558	0.882	24.032
5.110	3.000	0.477	0.523	0.746	20.427
5.300	3.000	0.630	0.370	0.695	19.089

R1_ampdiff	0.712	0.015	0.679	0.741	-	-	-	-
R1_meanpc	0.512	0.014	0.501	0.552	-	-	-	-
R1_maxpow	0.537	0.020	0.503	0.575	-	-	-	-
R1_meanfre	0.765	0.014	0.737	0.790	-	-	-	-
R1_meanfre	0.531	0.019	0.502	0.570	-	-	-	-

Indicators for comparison of PK	CImin	CImax	sign.

Figure 6.10 User interface of the program "Pk Tool" for computing prediction probability (P_k). Left panel refers to the data reading function. In the middle panel, above, is the class and indicators/features selection such as settings for computation and below, is the calculation and result output unit. Right panel indicates the Receiver Operating Characteristic Curve (ROC) only used for dichotomous classes (which is not the case). Results are saved as data sheets.

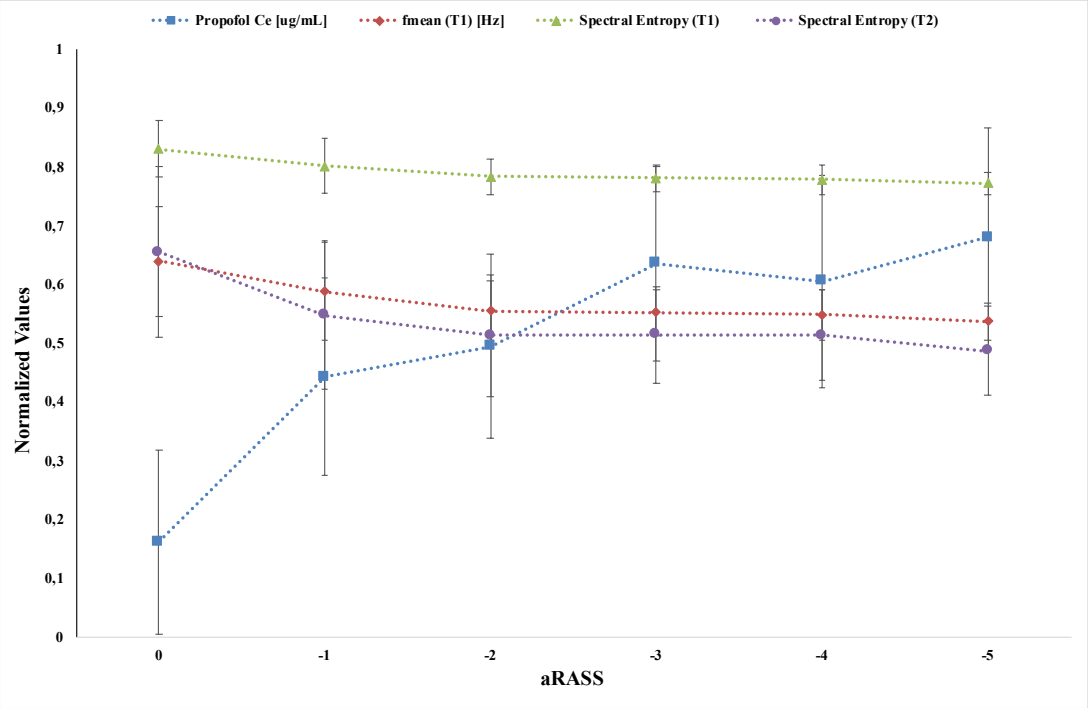


Figure 6.11 The adapted Richmond Agitation-Sedation Scale (aRASS) vs mean and standard deviation: 1) effect-site concentration (Ce) of propofol; 2) mean frequency (f_{mean} [Hz]) during the time window period T_1; 3) Spectral entropy during the time window period T_1; and 4) Spectral entropy during the time window period T_2.

The electromyographic-derived features in the time domain included the mean amplitude (V_{mean}), and the difference between the maximum and the mean amplitude (V_{diff}). Because R_2 and R_1 responses were abolished before LORP and, consequently, there was an insufficient number of data points, a frequency domain analysis was also performed. The electromyographic-derived features in the frequency domain included the mean power (P_{mean}), maximum power (Pmax), mean frequency (f_{mean}), power at mean frequency ($P_{meanfreq}$), median frequency (f_{median}), band power (P_{band}), total power (P_{total}), ratio between P_{total} and f_{median} (P_{total}/f_{median}), signal-to-noise (SNR), power bandwidth ($P_{bandwidth}$) and spectral entropy. These variables were selected as they are the most useful and popular frequency-domain features for electromyography analysis both in clinical and engineering applications.

The ability of the electromyographic-derived features to distinguish different levels of aRASS was assessed using prediction probability analysis. Spectral entropy, f_{mean}, f_{median} and $P_{bandwidth}$ during the T_1 time window period showed the best performance in detecting different levels of aRASS, as reflected by its higher P_k value, followed by spectral entropy and f_{mean} during the T_2 time window period. A statistically significant correlation (R>0.500) between aRASS (or propofol Ce concentration) and f_{mean} (T_1), f_{median} (T_1) and spectral entropy (T_1) period was also found. At low anesthetic concentration, the EMG frequency was high, and it slowed down as the drugs concentrations increased. Spectral entropy considers both the overall signal variability characteristics, which are naturally related to the spectral content, and the signal's complexity or irregularity [200]. For this reason, spectral entropy is known to be an excellent index to distinguish between consciousness and unconsciousness states during propofol anesthesia, even in the

presence of burst suppression [201]. f_{mean} and f_{median} are frequently used as the gold standard tool to detect force in the target muscles using EMG signals [202][203]. $P_{bandwidth}$ is supposed to be a good indicator of changes in the EMG signal when certain frequencies are lost, as is the case of the R_1 and R_2 component of the blink reflex, which have a particular signature. The effectiveness of spectral entropy, $f_{mean,}$ f_{median} and $P_{bandwidth}$ to distinguish the different levels of aRASS, resulted by the inhibition of EMG activity by muscle relaxation, is presented and confirmed in this study.

Another finding was that aRASS scale was strongly correlated with estimated propofol Ce concentrations, indicating that the clinical scale aRASS increased monotonically and positively with increasing estimated propofol Ce concentrations until LORP. This revealed an increasing deepening of anesthesia. This finding is in line with those published by Mourisse and colleagues [171][174] who have done a similar study using a different sedation scale and a different anesthetic protocol. In the work of Mourisse and colleagues, the group of patients received propofol in a stepwise deepening of anesthesia with different targets and only two minutes after reaching target effect-site concentrations, the blink reflexes, and depth of anesthesia scores were recorded. In the actual study, remifentanil infusion started with a Ce concentration target 2.5 μg/mL, and then patients received propofol at an infusion rate of 3.3 mL/kg/h, slowly and continuously, until LORP. Starting before the propofol infusion, the stimulation of the supraorbital nerve was recorded every 6 seconds in the actual study, and, for this reason, this method had more data to precisely identify the amount of propofol in the endpoints of interest.

Only the features that were both useful for predicting the aRASS scale ($P_k > 0.700$) and correlated significantly ($R>0.500$) with the propofol Ce concentration were used for the multinomial logistic regression model to predict LORP (defined as -5 in the aRASS scale). The results of the multinomial analysis showed a reasonable performance of the model, explaining almost 70% of the aRASS variance. The effects and contributions of each feature were not the same: propofol Ce concentration, f_{median} (T_1), spectral entropy during T_1, and spectral entropy during T_2 had a significant overall effect ($p < 0.05$) on the aRASS score, while V_{mean} (T_1), f_{median} (T_1) and f_{mean} (T_2) did not. The overall predictive accuracy for the model was 73.6%, suggesting that it is useful to predict LORP. The availability of accurate models for predicting the drug effect in patients undergoing general anesthesia is an important factor in producing a personalized drug infusion [204]. The developed model can be employed in model predictive control strategies for closed-loop anesthesia. This will help the anesthesiologists with the optimization of drug titration without overshoot and controlling the physiological functions. This automated system could also result in a reduction of the workload of the anesthesiologists.

A major drawback of this blink reflex method is that it is dependent on a normal neuromuscular transmission. The degree of relaxation can be estimated by stimulating the facial nerve and assessing the evoked response of that part of the orbicularis oculi muscle. The effect of muscle relaxants on the inferior part of the orbicularis oculi is still not known. Also, the blink reflex method, while promising, may imply that the anesthesiologists are stimulating the patient while simultaneously attempting to induce unconsciousness, even though it is a much smaller stimulation than shouting and taping (the standard in clinical practice).

Table 6.9: Prediction probabilities (P_k) values calculated between the adapted Richmond Agitation-Sedation Scale (aRASS) and the electromyography (EMG) extracted feature. Correlation coefficient R with aRASS and with propofol effect-site (Ce) concentration. T_1 and T_2 are time windows from 10 ms to 25 ms, and from 25 ms to 200 ms, respectively.

Parameter		aRASS		Correlation coefficient R with aRASS	Correlation coefficient R with propofol Ce concentration
		Pk	SE		
T_1	V_{mean}	0.712	0.015	0.420**	0.471**
	V_{diff}	0.712	0.015	-0.420**	-0.471**
	P_{mean}	0.512	0.014	0.025	-0.064**
	P_{max}	0.537	0.020	0.073	-0.010
	f_{mean}	0.765	0.014	-0.522**	-0.522**
	P_{fmean}	0.531	0.019	0.062	-0.022
	f_{median}	0.758	0.014	-0.507**	-0.504**
	P_{band}	0.529	0.019	0.058	-0.027
	P_{total}	0.512	0.014	0.025	-0.064
	P_{total}/f_{median}	0.538	0.020	0.075*	-0.007
	SNR	0.643	0.071	-0.114**	-0.052
	$P_{bandwidth}$	0.748	0.014	-0.487**	-0.482**
	Spectral entropy	0.771	0.013	-0.534**	-0.535**
T_2	V_{mean}	0.619	0.018	0.236**	0.201**
	V_{diff}	0.619	0.018	-0.236**	-0.201**
	P_{mean}	0.610	0.019	-0.216**	-0.430**
	P_{max}	0.578	0.019	-0.153**	-0.369**
	f_{mean}	0.721	0.015	-0.437**	-0.415**
	P_{fmean}	0.538	0.019	-0.064	-0.280**
	f_{median}	0.677	0.016	-0.353**	-0.334**
	P_{band}	0.599	0.018	-0.194**	-0.416**
	P_{total}	0.610	0.018	-0.216**	-0.438**
	P_{total}/f_{median}	0.557	0.019	-0.111**	-0.325**
	SNR	0.679	0.020	-0.387**	-0.452**
	$P_{bandwidth}$	0.605	0.017	-0.211**	-0.163**
	Spectral entropy	0.745	0.014	-0.485**	-0.464**

Prediction probability (P_k) values calculated with pooled data from all patients (n=25). The standard error (SE) is also shown. Rank correlation coefficient from pooled data of all patients (n=25) is shown.*Significant at the 0.05 level. **Significant at the 0.001 level. V_{mean}=mean amplitude; V_{diff}=difference between maximum and mean amplitude; P_{mean}=mean power; P_{max}=maximum power; f_{mean}=mean frequency; $P_{meanfrequency}$=power at mean frequency; f_{median}=median frequency; P_{band}=power band; P_{total}=total integrated of the spectrum; P_{total}/f_{median}=ratio between total power and median frequency; SNR=signal-to-noise ratio and $P_{bandwidth}$=power bandwidth.

The multinomial regression model was applied to a small sample size of the unconsciousness states in this study. In particular, the small number of unconsciousness states could be the cause of a not so high performance in detecting LORP. Even so, the performance of the developed model is relatively good and therefore, it is intended to be implemented for online estimation. However, preliminary studies should be conducted specially because of the computerization times the model can result.

Table 6.10: Likelihood ratio tests.

		-log likelihood	Chi-square	df	p-value
Intercept		1000.646	16.418	5	0.006
Propofol Ce		1313.757	329.529	5	<0.001
T_1	**V_{mean}**	993.034	8.806	5	0.117
	f_{median}	1002.125	17.897	5	0.003
	f_{median}	994.237	10.010	5	0.075
	$P_{bandwith}$	992.996	8.768	5	0.119
	Spectral entropy	1000.786	16.558	5	0.005
T_2	**f_{mean}**	994.827	10.599	5	0.060
	Spectral entropy	1001.268	17.040	5	0.004

V_{mean}=mean amplitude; f_{mean}=mean frequency; f_{median}=median frequency; $P_{bandwith}$=power bandwith; Ce=Effect-site Concentration.

Conclusions

By analyzing the electrically evoked blink reflex during the induction of general anesthesia with propofol and remifentanil, it was determined that there is enough relevant information to predict the state of unresponsiveness during the transition from consciousness to unconsciousness with a multinomial logistic model. A method that could allow for an automatic prediction/detection of LORP is a step forward for personalized medicine. With an accuracy of 73.6%, this model can help to greatly reduce the overwhelming variability observed between patients and avoid many cases of overdosing and associated risks. To the best knowledge, no studies have been conducted on LORP prediction using the presented approach.

Despite the results, it would be accurate if a larger sample size was obtained for applying the multinomial regression model or any other prediction model to analyze the relation between the aRASS and the EMG effect reflected in extracted features. Further research should investigate the impact of remifentanil on such a technique.

Nevertheless, the method of electromyographic recording of the electrically evoked blink reflex in patients submitted to general anesthesia and in the continuum to unconsciousness showed to be a possible method to continuously monitor the EMG, in awake, sedated or unconsciousness patients, during the onset to unconsciousness, and in a real scenario in which clinical anesthesia takes place every day. Patients also found the stimuli to be easily tolerable. Devices using this technique could turn this method into a clinical routine way of monitoring the transition to unconsciousness.

In the future, it is intended to add other variables to feed the model, such as heart rate, blood pressure, and electroencephalogram. It is planned to use those variables to build an adaptive model that deals simultaneously with the variabilities in the clinical response of the patients and with the drug interactions. Additionally, it is thought to use different EMG equipment for more robustness.

7 CONCLUSIONS AND FUTURE WORK

General anesthesia has three main components: analgesia, hypnosis, and immobility. To actuate most appropriately in respect of the three referred components, anesthesiologists need to be aware of the real state of the patient in every step of the anesthesia process. Given the vast amount of information that an anesthesiologist needs to manage and process in the operating room, the error is eminent while performing other tasks. The anesthesiologist's main objective is to provide the correct amount of drug for each component to achieve the adequate and desired state. While immobility is not always present, the hypnosis and analgesia components are still present, depending on the surgical intervention. While specific drug classes target specific clinical endpoints, i.e., hypnotics for hypnosis and 'analgesics' (opioids) for 'analgesia', opioids also have sedative effects, and propofol also has analgesic properties. Hypnosis is the most fascinating component of general anesthesia. The mechanisms leading to anesthetic-induced unconsciousness are complex and constitute a fundamental, unresolved question. Much evidence suggests that both consciousness and anesthetic-induced unconsciousness depend on high-order processes of the brain. Several PK-PD models exist for propofol. Some have been integrated into TCI systems, which facilitates clinical practice and maintenance of intravenous anesthesia. Due to some limitations of the existent models, clinicians should use the model and methods with which they are most familiar. The Schnider model, although not perfect, is recommended for TCI and advisory drug displays. However, to achieve precise propofol titration, the quantification of pharmacodynamic must obtain a personalized and tailored approach. Gathering the concept of personalized anesthesia and its hypnotic component suggests an important question: developing systems that can provide the correct propofol dose to each patient during induction and maintenance of general anesthesia. Induction of anesthesia is still widely performed in the way it was when intravenous agents became available, which is a quick manual administration of a bolus based on the patient's weight. Few scientific evidence or pharmacology knowledge has been used to change this practice. It is believed that bringing together information from both PK-PD during the induction phase might bring the possibility to improve drug delivery during maintenance and thus be important to one

achieve the personalized hypnotic effect. Assisting in the titration of propofol during the maintenance phase of general anesthesia is possible due to the currently available DOA monitors, however, for the induction of anesthesia, such monitors are not the best choice as they have an excessive processing time delay. It is essential to administer propofol slowly for induction to give the exact amount required for LOC, which it is believed to be an ideal end-point to stop the infusion of propofol and titrate it accordingly to the DOA index, which should result in less anesthetic being required and therefore, result in an attenuation of the side effects from overdosing. If one accepts that performing propofol induction through a slow-rate infusion offers an advantage, one faces how to assess LOC's moment during the induction.

Thus, the motivation of this work was to develop a solution that allows for the objectively and promptly detection of the moment of LOC during the transition between consciousness and unconsciousness in the induction phase of general anesthesia in patients subjected to neurosurgeries.

This thesis conveys both the importance of personalizing anesthesia and the challenges encountered by anesthesiologists in its pursuit.

Unconsciousness is not always a straightforward behavioral state, as one might assume. The same drug can act on multiple brain sites and various drugs can act synergistically in one compartment. Moreover, it is necessary to integrate wide inter-patient variability.

This thesis is a culmination of several works that explore novel methods of measuring the loss of consciousness. For the detection of unconsciousness, studies with electroencephalography and studies with electromyography were performed.

Regarding the studies with electroencephalography, two main approaches were employed: an examination of EEG signatures associated with the transition from consciousness to unconsciousness and implementation of neural networks to learn the EEG signal and detect the precise moment of loss of consciousness. Both studies were performed during the induction of general anesthesia with propofol and remifentanil. Changes in the EEG signatures were observed during the transition from consciousness to unconsciousness. Data were analyzed with multitaper spectrograms, and the results showed that as the patients progressed from conscious to unconscious, gamma power decreased, and alpha and delta power increased. This served as evidence to create a robust and well-supported model for tracking the dynamic changes between conscious and unconscious states. With this in mind, a convolutional neural network model was implemented and applied to the raw EEG signals of 50 patients. The model was able to identify patients transitioning to unconsciousness with a mean accuracy of almost 98%, which constituted a solid base for us to argue that EEG has enough relevant information to detect the state of unconsciousness during the transition from consciousness to unconsciousness. Regardless of these preliminary results, a more considerable amount of data is necessary to train and test the neural network. More studies are also needed to study the impact of remifentanil on such a system and with different anesthesia protocols with other drugs. Despite that, it is believed that the developed neural network model (NNM) would be valid outside the combination opioid-propofol and anesthesia protocol. The model only uses the EEG signal and its information; therefore, the amount of infusion profiles should not change the performance. This is valid

with other anesthetic drugs that affect the central nervous system in similar ways, in monitors such as BIS, which also use processed EEG and work well for anesthesia maintenance.

Regarding the studies with electromyography, the following approaches were employed: evaluation of neurophysiologic-derived parameters of EMG records of electrically evoked blink reflex on the identification of LOC, and prediction probability analysis and multinomial logistic modeling to predict the concentration required for LOC. It was shown that neurophysiologically-derived parameters of EMG records of electrically evoked blink reflex could be used as surrogates of the sedation/anesthesia scale to provide an objective end-point of the cortical and brainstem effects of propofol in the continuum to unconsciousness, and in a real scenario in which clinical anesthesia takes place every day. Based on these findings, although blink reflex was an indicator of immobility, it was not useful in precisely determining the absence of consciousness. However, one can argue that, due to overshooting, the proposed moment to stop the propofol infusion would be after the patient loses the R_1 component of the blink reflex. This would then lead to a subsequent increase in the effect-site concentration from the already circulating plasma propofol and achieve a higher concentration that may be capable of abolishing the behavioral reflex, the target endpoint. If this subsequent increase was not enough, the infusion could be resumed for an increased dose. In this study, it was also observed that the R_2 component of the blink reflex was quickly abolished, and the R_1 component was abolished too soon, which may result in an insufficient number of data points or hidden information. It was decided to analyze the electromyographic-derived parameters in the frequency domain. It was found some relevant features able to distinguish different levels of sedation/anesthesia using prediction probability analysis. These features were used in a multinomial logistic regression model to predict the unconsciousness level. The multinomial analysis results showed an overall predictive accuracy for the model of 73.6%, suggesting that it was useful to predict the loss of consciousness. A method that could allow for an automatic prediction/detection of loss of consciousness is a step forward for personalized medicine. The presented model can help to greatly reduce the overwhelming variability observed between patients and avoid many cases of overdosing and associated risks. No studies have been conducted on the loss of consciousness prediction using the presented approach to the best knowledge. A limitation of the blink reflex method was that it was dependent on a normal neuromuscular transmission. The degree of relaxation can be estimated by stimulating the facial nerve and assessing the evoked response of that part of the orbicularis oculi muscle. The effect of muscle relaxants on the inferior part of the orbicularis oculi was still not known. Also, the multinomial regression model was applied to a small sample size of the unconsciousness states in this study. In particular, the small number of unconsciousness states could cause a not so high performance in detecting loss of consciousness.

The foundation of this research project was defined, considering the routine clinical practice of general anesthesia. The main drawback of this work, which is transversal to all the studies presented here, is that during the clinical approach of general anesthesia, in order to assess the levels of sedation/anesthesia, anesthesiologists are stimulating the patient while simultaneously attempting to induce unconsciousness. This seems counterintuitive, but it was believed that methods such as the developed one could replace that in the future. Another limitation is that it was analyzed the effect-site concentrations of propofol. Having

measured real plasma concentrations would have provided stronger evidence in favor of or against the conclusions. Despite this, the electroencephalography and electromyography-based methods provided objective and reliable approaches in detecting the loss of consciousness.

Recovery of consciousness was also a topic of this research. Usually, this process is considered passive as emergence from anesthesia is viewed as the inverse of induction while anesthetic drugs are eliminated from their sites of action within the central nervous system. Findings in general anesthesia support the presence of hysteresis during changes in states of consciousness and unconsciousness in humans, also known as neural inertia.

Based on promising results, a patent is thought to be submitted for a sensor capable of automatically measuring the corneal reflex while integrating EEG monitoring. Nevertheless, the idea is that users will have the option to discard the automatic control and manually titrate the propofol infusion. It is up to the anesthesiologist to integrate the information available in the sensors or monitors to create a more complete picture of how each patient will respond to and recover from anesthesia.

The interest in personalizing anesthesia and the promising findings from this research have led to the constitution of a spin-off company to integrate the aforementioned technologies. A sensor is currently being developed in collaboration with another company, and a clinical trial will be ensued to assess the efficacy of this novel method.

7.1 Future Work

To better understand the implications of the electroencephalographic and electromyographic-based methods to detect LOC, further studies should be performed to show the potential and applicability of those in routine anesthesia. Concerning the EEG signatures study, a dynamic state-space model framework for the simultaneous characterization of involuntary and monitored physiological dynamics during the gradual transition from consciousness to unconsciousness is intended to be developed. The simultaneous acquisition of three modalities of observations related to the onset of unconsciousness would also be performed: behavioral responses, EMG activity, and EEG spectral power. Combining the information from all of these different types of observations, a robust and well-supported estimate for tracking the dynamic changes in a subject's wakefulness as they enter into the unconsciousness state could be created. Regarding the neural network model applied to the raw EEG, future research should focus on collecting hundreds of new EEG labeled cases that can be used to re-train the model and improve accuracy even further in terms of consistency and confidence interval levels. It is also intended to add other variables to feed the neural network, such as heart rate, blood pressure, and electromyography. Additionally, it is planned to use different EEG equipment for additional robustness. The developed approach was implemented on an internal cloud, and it is intended to use it in real-time during medical procedures. In relation to the model build based on the EMG-derived features of the blink reflex, the plan is to add more variables and use those variables to build an adaptive model that deals simultaneously with the variabilities in the clinical response

of the patients and with the drug interactions. Additionally, it is planned to use different EMG equipment for more robustness.

Crucial future work recommendations include a larger population sample and a controlled trial to test testing and validate the approaches. This research may address the analysis of blood samples to validate the plasma concentration estimated and include the intra and inter-individual variability assessment to optimize the hypnotic effect and improve the accuracy of the developed methods.

Finally, having a system capable of integrating a method that automatically measures the corneal reflex while integrating EEG monitoring will have an enormous impact on anesthesia worldwide.

In conclusion, the main contribution of the research conducted in this PhD was the development of methods for automatically detecting loss of consciousness during the induction phase of general anesthesia. In addition to presenting knowledge in drug-induced loss of consciousness, it brings important benefits to anesthesia, by determining the hypnotic amount required for each patient and providing an important information to guide the infusion rate required to maintain adequate level of anesthesia, ensuring a safe and an effective care, reducing the anesthesiologists' workload, as well as avoiding overdosage or intraoperative awareness.

Ultimately, through the combination of loss of consciousness detection and a closed-loop control technique, it may be possible to individualize the propofol drug delivery and optimize the maintenance during surgical procedures.

8 REFERENCES

[1] P. S. Garcia, S. E. Kolesky, and A. Jenkins, "General anesthetic actions on GABA(A) receptors.," *Curr. Neuropharmacol.*, vol. 8, no. 1, pp. 2–9, Mar. 2010, doi: 10.2174/157015910790909502.

[2] G. A. Mashour, "Top-down mechanisms of anesthetic-induced unconsciousness.," *Front. Syst. Neurosci.*, vol. 8, p. 115, Jan. 2014, doi: 10.3389/fnsys.2014.00115.

[3] M. Beer, J. Schüttler, and H. Schwilden, *Modern anesthetics*, vol. 182. Berlin, Heidelberg: Springer, 2008.

[4] C. S. Nunes, T. Mendonca, S. Bras, D. A. Ferreira, and P. Amorim, "Modeling Anesthetic Drugs' Pharmacodynamic Interaction on the Bispectral Index of the EEG: the Influence of Heart Rate," in *2007 29th Annual International Conference of the IEEE Engineering in Medicine and Biology Society*, 2007, vol. 2007, pp. 6479–6482, doi: 10.1109/IEMBS.2007.4353843.

[5] T. Kazama *et al.*, "Investigation of Effective Anesthesia Induction Doses Using a Wide Range of Infusion Rates with Undiluted and Diluted Propofol," *Anesthesiology*, vol. 92, no. 4, pp. 1017–1028, Apr. 2000, doi: 10.1097/00000542-200004000-00019.

[6] L. Bosch, J. Fernández-Candil, A. León, and P. L. Gambús, "Influencia de la anestesia general sobre el tronco encefálico," *Rev. Esp. Anestesiol. Reanim.*, vol. 64, no. 3, pp. 157–167, Mar. 2017, doi: 10.1016/j.redar.2016.09.005.

[7] K. Leslie *et al.*, "Prediction of Movement during Propofol/Nitrous Oxide Anesthesia," *Anesthesiology*, vol. 84, no. 1, pp. 52–63, Jan. 1996, doi: 10.1097/00000542-199601000-00006.

[8] J. B. Bijker, W. A. Van Klei, T. H. Kappen, L. Van Wolfswinkel, K. G. M. Moons, and C. J. Kalkman, "Incidence of intraoperative hypotension as a function of the chosen definition: Literature definitions applied to a retrospective cohort using automated data collection," *Anesthesiology*, 2007, doi: 10.1097/01.anes.0000270724.40897.8e.

[9] "Portal da Saúde, Mds Portugal." [Online]. Available: http://www.portaldasaude.pt/portal/conteudos/informacoes+uteis/lista+de+inscritos+para+cirurgia/balanco+1sem+2012.htm.

[10] P. Lemos *et al.*, "2017 Census: are there enough anaesthesiologists in Portugal?," *Acta Med. Port.*, vol. 31, no. 5, pp. 254–264, 2018.

[11] M. M. Ghoneim, "Incidence of and risk factors for awareness during anaesthesia.," *Best Pract. Res. Clin. Anaesthesiol.*, vol. 21, no. 3, pp. 327–43, Sep. 2007.

[12] V. Tarnal, P. E. Vlisides, and G. A. Mashour, "The Neurobiology of Anesthetic Emergence.," *J. Neurosurg. Anesthesiol.*, vol. 28, no. 3, pp. 250–5, Aug. 2015, doi: 10.1097/ANA.0000000000000212.

[13] E. I. Eger, "Characteristics of anesthetic agents used for induction and maintenance of general anesthesia.," *Am. J. Health. Syst. Pharm.*, vol. 61 Suppl 4, pp. S3-10, Oct. 2004.

[14] T. W. Schnider *et al.*, "The influence of age on propofol pharmacodynamics.," *Anesthesiology*, vol. 90, no. 6, pp. 1502–16, Jun. 1999.

[15] "Diprivan 10 mg/ml (1%) emulsion for injection or infusion - Summary of Product Characteristics (SmPC) - (eMC)." .

[16] T. Kazama, K. Ikeda, K. Morita, T. Ikeda, M. Kikura, and S. Sato, “Relation between initial blood distribution volume and propofol induction dose requirement.,” *Anesthesiology*, vol. 94, no. 2, pp. 205–10, Feb. 2001.

[17] Y. U. Adachi, M. Satomoto, H. Higuchi, and K. Watanabe, “The determinants of propofol induction time in anesthesia,” *Korean J. Anesthesiol.*, vol. 65, no. 2, p. 121, Aug. 2013, doi: 10.4097/kjae.2013.65.2.121.

[18] J. Blum, E. Kochs, N. Forster, and G. Schneider, “The influence of injection rate on the hypnotic effect of propofol during anesthesia: a randomized trial.,” *PLoS Clin. Trials*, vol. 1, no. 3, p. e17, Jul. 2006, doi: 10.1371/journal.pctr.0010017.

[19] J. E. Peacock, R. P. Lewis, C. S. Reilly, and W. S. Nimmo, “Effect of different rates of infusion of propofol for induction of anaesthesia in elderly patients.,” *Br. J. Anaesth.*, vol. 65, no. 3, pp. 346–52, Sep. 1990.

[20] A. C. Ferreira, C. S. Nunes, A. I. Castro, A. L. Ferreira, and P. Amorim, “Propofol Requirements for Anesthesia Induction Show Wide Individual Variability, Independently of Age, Gender, Weight and Height,” in *Proceedings from the American Society of Anesthesiologists*, 2015.

[21] G. A. Mashour *et al.*, “Prevention of intraoperative awareness with explicit recall in an unselected surgical population: a randomized comparative effectiveness trial.,” *Anesthesiology*, vol. 117, no. 4, pp. 717–25, Oct. 2012, doi: 10.1097/ALN.0b013e31826904a6.

[22] T. G. Monk, V. Saini, B. C. Weldon, and J. C. Sigl, “Anesthetic Management and One-Year Mortality After Noncardiac Surgery,” *Anesth. Analg.*, vol. 100, no. 1, pp. 4–10, Jan. 2005, doi: 10.1213/01.ANE.0000147519.82841.5E.

[23] M.-L. Lindholm *et al.*, “Mortality Within 2 Years After Surgery in Relation to Low Intraoperative Bispectral Index Values and Preexisting Malignant Disease,” *Anesth. Analg.*, vol. 108, no. 2, pp. 508–12, Feb. 2009, doi: 10.1213/ane.0b013e31818f603c.

[24] S. Chaudhri, M. White, and G. N. Kenny, “Induction of anaesthesia with propofol using a target-controlled infusion system.,” *Anaesthesia*, vol. 47, no. 7, pp. 551–3, Jul. 1992.

[25] A. R. Absalom, J. I. B. Glen, G. J. C. Zwart, T. W. Schnider, and M. M. R. F. Struys, “Target-Controlled Infusion: A Mature Technology.,” *Anesth. Analg.*, vol. 122, no. 1, pp. 70–8, Jan. 2016, doi: 10.1213/ANE.0000000000001009.

[26] E. N. Brown, R. Lydic, and N. D. Schiff, “General anesthesia, sleep, and coma.,” *N. Engl. J. Med.*, vol. 363, no. 27, pp. 2638–50, Dec. 2010, doi: 10.1056/NEJMra0808281.

[27] B. Marsh, M. White, N. Morton, and G. N. C. Kenny, “Pharmacokinetic model driven infusion of propofol in children,” *Br. J. Anaesth.*, vol. 67, no. 1, pp. 41–48, 1991, doi: 10.1093/bja/67.1.41.

[28] T. W. Schnider *et al.*, “The influence of method of administration and covariates on the pharmacokinetics of propofol in adult volunteers.,” *Anesthesiology*, vol. 88, no. 5, pp. 1170–82, May 1998.

[29] C. F. Minto *et al.*, “Influence of age and gender on the pharmacokinetics and pharmacodynamics of remifentanil. I. Model development.,” *Anesthesiology*, vol. 86, no. 1, pp. 10–23, Jan. 1997.

[30] S. L. Shafer, J. R. Varvel, N. Aziz, and J. C. Scott, “Pharmacokinetics of fentanyl administered by computer-controlled infusion pump.,” *Anesthesiology*, vol. 73, no. 6, pp. 1091–102, Dec. 1990.

[31] R. J. Hudson, R. G. Bergstrom, I. R. Thomson, M. A. Sabourin, M. Rosenbloom, and L. Strunin, “Pharmacokinetics of sufentanil in patients undergoing abdominal aortic surgery.,” *Anesthesiology*, vol. 70, no. 3, pp. 426–31, Mar. 1989.

[32] R. Mihai, S. Scott, and T. M. Cook, “Litigation related to inadequate anaesthesia: an analysis of claims against the NHS in England 1995-2007,” *Anaesthesia*, vol. 64, no. 8, pp. 829–835, Aug. 2009, doi: 10.1111/j.1365-2044.2009.05912.x.

[33] J. Vuyk, M. J. Mertens, E. Olofsen, A. G. Burm, and J. G. Bovill, “Propofol anesthesia and rational opioid selection: determination of optimal EC50-EC95 propofol-opioid concentrations that assure adequate anesthesia and a rapid return of consciousness.,” *Anesthesiology*, vol. 87, no. 6, pp. 1549–62, Dec. 1997.

[34] Y. U. Adachi, K. Watanabe, H. Higuchi, and T. Satoh, “The determinants of propofol induction of anesthesia dose.,” *Anesth. Analg.*, vol. 92, no. 3, pp. 656–61, Mar. 2001.

[35] B. Escontrela Rodríguez, A. Gago Martínez, I. Merino Julián, and A. Martínez Ruiz, *La entropía espectral en la monitorización de la profundidad de la anestesia*, vol. 63, no. 8. Elsevier, 2016, pp. 471–478.

[36] D. A. Chernik *et al.*, “Validity and reliability of the Observer’s Assessment of Alertness/Sedation Scale: study with intravenous midazolam.,” *J. Clin. Psychopharmacol.*, vol. 10, no. 4, pp. 244–

51, Aug. 1990.
[37] G. H. Klem, H. O. Lüders, H. H. Jasper, and C. Elger, “The ten-twenty electrode system of the International Federation. The International Federation of Clinical Neurophysiology.,” *Electroencephalogr. Clin. Neurophysiol. Suppl.*, vol. 52, pp. 3–6, 1999.
[38] Y. Punjasawadwong, W. Chau-in, M. Laopaiboon, S. Punjasawadwong, and P. Pin-on, “Processed electroencephalogram and evoked potential techniques for amelioration of postoperative delirium and cognitive dysfunction following non-cardiac and non-neurosurgical procedures in adults,” *Cochrane Database Syst. Rev.*, vol. 5, p. CD011283, May 2018, doi: 10.1002/14651858.CD011283.pub2.
[39] B. Musizza and S. Ribaric, *Monitoring the depth of anaesthesia*, vol. 10, no. 12. 2010, pp. 10896–10935.
[40] G. D. Puri *et al.*, “A Multicenter Evaluation of a Closed-Loop Anesthesia Delivery System,” *Anesth. Analg.*, vol. 122, no. 1, pp. 106–114, Jan. 2016, doi: 10.1213/ANE.0000000000000769.
[41] T. De Smet, M. M. R. F. Struys, M. M. Neckebroek, K. Van den Hauwe, S. Bonte, and E. P. Mortier, “The Accuracy and Clinical Feasibility of a New Bayesian-Based Closed-Loop Control System for Propofol Administration Using the Bispectral Index as a Controlled Variable,” *Anesth. Analg.*, vol. 107, no. 4, pp. 1200–1210, Oct. 2008, doi: 10.1213/ane.0b013e31817bd1a6.
[42] C. Zaouter *et al.*, “A novel system for automated propofol sedation: hybrid sedation system (HSS),” *J. Clin. Monit. Comput.*, vol. 31, no. 2, pp. 309–317, Apr. 2017, doi: 10.1007/s10877-016-9858-0.
[43] N. Liu *et al.*, “Closed-Loop Coadministration of Propofol and Remifentanil Guided by Bispectral Index,” *Anesth. Analg.*, vol. 112, no. 3, pp. 546–557, Mar. 2011, doi: 10.1213/ANE.0b013e318205680b.
[44] T. M. Hemmerling, S. Charabati, C. Zaouter, C. Minardi, and P. A. Mathieu, “A randomized controlled trial demonstrates that a novel closed-loop propofol system performs better hypnosis control than manual administration,” *Can. J. Anesth. Can. d’anesthésie*, vol. 57, no. 8, pp. 725–735, Aug. 2010, doi: 10.1007/s12630-010-9335-z.
[45] T. M. Hemmerling, E. Arbeid, M. Wehbe, S. Cyr, R. Taddei, and C. Zaouter, “Evaluation of a novel closed-loop total intravenous anaesthesia drug delivery system: a randomized controlled trial,” *Br. J. Anaesth.*, vol. 110, no. 6, pp. 1031–1039, Jun. 2013, doi: 10.1093/bja/aet001.
[46] Y. Liu *et al.*, “Closed-Loop Control Better than Open-Loop Control of Profofol TCI Guided by BIS: A Randomized, Controlled, Multicenter Clinical Trial to Evaluate the CONCERT-CL Closed-Loop System,” *PLoS One*, vol. 10, no. 4, p. e0123862, Apr. 2015, doi: 10.1371/journal.pone.0123862.
[47] A. Morley, J. Derrick, P. Mainland, B. B. Lee, and T. G. Short, “Closed loop control of anaesthesia: an assessment of the bispectral index as the target of control.,” *Anaesthesia*, vol. 55, no. 10, pp. 953–9, Oct. 2000.
[48] L. Pasin *et al.*, “Closed-Loop Delivery Systems Versus Manually Controlled Administration of Total IV Anesthesia,” *Anesth. Analg.*, vol. 124, no. 2, pp. 456–464, Feb. 2017, doi: 10.1213/ANE.0000000000001394.
[49] P. L. Purdon *et al.*, “Electroencephalogram signatures of loss and recovery of consciousness from propofol.,” *Proc. Natl. Acad. Sci. U. S. A.*, vol. 110, no. 12, pp. E1142-51, Mar. 2013, doi: 10.1073/pnas.1221180110.
[50] Z. Xu *et al.*, “C50 for propofol-remifentanil target-controlled infusion and bispectral index at loss of consciousness and response to painful stimulus in Chinese patients: a multicenter clinical trial.,” *Anesth. Analg.*, vol. 108, no. 2, pp. 478–83, Feb. 2009, doi: 10.1213/ane.0b013e31818f8a30.
[51] Z. Chen, D.-H. Shao, and L.-H. Hang, “Effects of dexmedetomidine on performance of bispectral index as an indicator of loss of consciousness during propofol administration.,” *Swiss Med. Wkly.*, vol. 143, p. w13762, Jan. 2013, doi: 10.4414/smw.2013.13762.
[52] J. Gao *et al.*, “Evaluation of entropy for monitoring the depth of anesthesia compared with bispectral index: a multicenter clinical trial.,” *Chin. Med. J. (Engl).*, vol. 125, no. 8, pp. 1389–92, Apr. 2012.
[53] C. Lysakowski *et al.*, “Bispectral and spectral entropy indices at propofol-induced loss of consciousness in young and elderly patients.,” *Br. J. Anaesth.*, vol. 103, no. 3, pp. 387–93, Sep. 2009, doi: 10.1093/bja/aep162.
[54] K. Kaneda, S. Yamashita, S. Woo, and T.-H. Han, “Population Pharmacokinetics and

Pharmacodynamics of Brief Etomidate Infusion in Healthy Volunteers," *J. Clin. Pharmacol.*, vol. 51, no. 4, pp. 482–491, Apr. 2011, doi: 10.1177/0091270010369242.

[55] M. J. Coppens, L. F. M. Versichelen, E. P. Mortier, and M. M. R. F. Struys, "Do we need inhaled anaesthetics to blunt arousal, haemodynamic responses to intubation after i.v. induction with propofol, remifentanil, rocuronium?," *Br. J. Anaesth.*, vol. 97, no. 6, pp. 835–41, Dec. 2006, doi: 10.1093/bja/ael254.

[56] K. Kanata, S. Sakura, H. Kushizaki, T. Nakatani, and Y. Saito, "Effects of epidural anesthesia with 0.2% and 1% ropivacaine on predicted propofol concentrations and bispectral index values at three clinical end points.," *J. Clin. Anesth.*, vol. 18, no. 6, pp. 409–14, Sep. 2006, doi: 10.1016/j.jclinane.2006.01.004.

[57] D. Karalapillai, K. Leslie, A. Umranikar, and A. R. Bjorksten, "Nitrous oxide and anesthetic requirement for loss of response to command during propofol anesthesia.," *Anesth. Analg.*, vol. 102, no. 4, pp. 1088–93, Apr. 2006, doi: 10.1213/01.ane.0000198672.05639.0a.

[58] C. González, M. Mendes, P. Amorim, J. Mendes, and C. Nunes, "Usefulness of brain signals for the detection of loss of consciousness in anesthesia: overview of the problem and results from a clinical study," in *Biosignals*, 2009.

[59] W. D. Mi, T. Sakai, T. Kudo, M. Kudo, and A. Matsuki, "Performance of bispectral index and auditory evoked potential monitors in detecting loss of consciousness during anaesthetic induction with propofol with and without fentanyl.," *Eur. J. Anaesthesiol.*, vol. 21, no. 10, pp. 807–11, Oct. 2004.

[60] C. Lysakowski *et al.*, "Effects of fentanyl, alfentanil, remifentanil and sufentanil on loss of consciousness and bispectral index during propofol induction of anaesthesia.," *Br. J. Anaesth.*, vol. 86, no. 4, pp. 523–7, Apr. 2001, doi: 10.1093/bja/86.4.523.

[61] L. I. Cortínez, A. E. Delfino, R. Fuentes, and H. R. Muioz, "Performance of the Cerebral State Index During Increasing Levels of Propofol Anesthesia: A Comparison with the Bispectral Index," *Anesth. Analg.*, vol. 104, no. 3, pp. 605–610, Mar. 2007, doi: 10.1213/01.ane.0000255152.96354.17.

[62] N. Liu, T. Chazot, I. Huybrechts, J.-D. Law-Koune, L. Barvais, and M. Fischler, "The influence of a muscle relaxant bolus on bispectral and datex-ohmeda entropy values during propofol-remifentanil induced loss of consciousness.," *Anesth. Analg.*, vol. 101, no. 6, pp. 1713–8, Dec. 2005, doi: 10.1213/01.ANE.0000184038.49429.8F.

[63] H. Kokki, J. Wennervirta, M. Laisalmi, and A. Vakkuri, "Regular tramadol use does not affect the propofol dose requirement for induction of anaesthesia.," *Eur. J. Anaesthesiol.*, vol. 24, no. 9, pp. 776–81, Sep. 2007, doi: 10.1017/S0265021507000439.

[64] R. E. Anderson and J. G. Jakobsson, "Entropy of EEG during anaesthetic induction: a comparative study with propofol or nitrous oxide as sole agent.," *Br. J. Anaesth.*, vol. 92, no. 2, pp. 167–70, Feb. 2004.

[65] G. Schneider, S. Heglmeier, J. Schneider, G. Tempel, and E. F. Kochs, "Patient State Index (PSI) measures depth of sedation in intensive care patients.," *Intensive Care Med.*, vol. 30, no. 2, pp. 213–6, Feb. 2004, doi: 10.1007/s00134-003-2092-5.

[66] M. H. H. Kuizenga *et al.*, "Test of neural inertia in humans during general anaesthesia," *Br. J. Anaesth.*, vol. 120, no. 3, pp. 525–536, Mar. 2018, doi: 10.1016/j.bja.2017.11.072.

[67] S. Pilge, J. Blum, E. F. Kochs, S.-A. Schöniger, M. Kreuzer, and G. Schneider, "Does the cerebral state index separate consciousness from unconsciousness?," *Anesth. Analg.*, vol. 113, no. 6, pp. 1403–10, Dec. 2011, doi: 10.1213/ANE.0b013e31823007cd.

[68] P. O. Sepúlveda, L. I. Cortínez, A. Recart, and H. R. Muñoz, "Predictive ability of propofol effect-site concentrations during fast and slow infusion rates.," *Acta Anaesthesiol. Scand.*, vol. 54, no. 4, pp. 447–52, Apr. 2010, doi: 10.1111/j.1399-6576.2009.02183.x.

[69] R. E. Anderson, G. Barr, and J. G. Jakobsson, "Cerebral state index during anaesthetic induction: a comparative study with propofol or nitrous oxide.," *Acta Anaesthesiol. Scand.*, vol. 49, no. 6, pp. 750–3, Jul. 2005, doi: 10.1111/j.1399-6576.2005.00737.x.

[70] F. Weber, M. Gruber, and K. Taeger, "The correlation of the Narcotrend Index and classical electroencephalographic parameters with endtidal desflurane concentrations and hemodynamic parameters in different age groups.," *Paediatr. Anaesth.*, vol. 15, no. 5, pp. 378–84, May 2005, doi: 10.1111/j.1460-9592.2005.01465.x.

[71] H. Tan, L. Cao, W. Huang, Z. Zhong, W. Lin, and W. Zeng, "[Comparison of sevoflurane and propofol in combined anesthesia induction with remifentanil for tracheal intubation with

fiberoptic bronchoscope].," *Nan Fang Yi Ke Da Xue Xue Bao*, vol. 30, no. 8, pp. 1857–9, Aug. 2010.

[72] H. Litvan, P. Cotaimich, M. Revuelta, J. Galán, J. A. Fernández, and J. M. Campos, "Comparison of the Index of Consciousness (IoC) and the Auditory Evoked Potentials Index (AAI) during induction of general anaesthesia," *Eur. J. Anaesthesiol.*, vol. 23, p. A-81, 2006.

[73] U. Melia *et al.*, "Comparison of the qCON and qNOX indices for the assessment of unconsciousness level and noxious stimulation response during surgery," *J. Clin. Monit. Comput.*, vol. 31, no. 6, pp. 1273–1281, Dec. 2017, doi: 10.1007/s10877-016-9948-z.

[74] E. W. Jensen *et al.*, "Monitoring hypnotic effect and nociception with two EEG-derived indices, qCON and qNOX, during general anaesthesia," *Acta Anaesthesiol. Scand.*, vol. 58, no. 8, pp. 933–941, Sep. 2014, doi: 10.1111/aas.12359.

[75] J. Tang, H. Ma, P. F. White, and R. H. Wender, "Comparative Evaluation of Auditory Evoked Potential Index (AAI) and Bispectral Index^{TM} (BIS^{TM}) Values during Induction and Emergence from Ambulatory Anesthesia," *Am. Soc. Anesthesiol.*, vol. A347, 2003.

[76] M. M. R. F. Struys *et al.*, "Performance of the ARX-derived auditory evoked potential index as an indicator of anesthetic depth: a comparison with bispectral index and hemodynamic measures during propofol administration.," *Anesthesiology*, vol. 96, no. 4, pp. 803–16, Apr. 2002.

[77] L. Muñoz, J. J. Arévalo, L. E. Reyes, and C. E. Balaguera, "Remifentanilo versus propofol con infusión controlada a objetivo en sitio efecto para la sedación de pacientes durante procedimientos endoscópicos gastrointestinales: ensayo clínico controlado aleatorizado," *Rev. Colomb. Anestesiol.*, vol. 41, no. 2, pp. 114–119, Apr. 2013, doi: 10.1016/J.RCA.2012.11.001.

[78] C. F. Minto, T. W. Schnider, and S. L. Shafer, "Pharmacokinetics and pharmacodynamics of remifentanil. II. Model application.," *Anesthesiology*, vol. 86, no. 1, pp. 24–33, Jan. 1997.

[79] H. Iwakiri, N. Nishihara, O. Nagata, T. Matsukawa, M. Ozaki, and D. I. Sessler, "Individual effect-site concentrations of propofol are similar at loss of consciousness and at awakening.," *Anesth. Analg.*, vol. 100, no. 1, pp. 107–10, Jan. 2005, doi: 10.1213/01.ANE.0000139358.15909.EA.

[80] A. Castro, N. Bessan, F. Lobo, C. S. Nunes, and P. Amorim, "The higher the Propofol Concentration the Larger its Difference to the Concentrations Required at Maintenance, Using TCI and BIS Guided Anaesthesia," *Eur. J. Anaesthesiol.*, vol. 25, p. 150, 2008.

[81] K. Haensch, A. Schultz, T. Krauss, U. Grouven, and B. Schultz, "Women need more propofol than men during EEG-monitored total intravenous anaesthesia," *Biomed. Tech.*, vol. 54, no. 2, pp. 76–82, 2009.

[82] A. Graca, T. Leal, A. Castro, P. Amorim, and E. Amadeu, "Women require more propofol for LOC (Loss of consciousness) than men," in *European Journal of Anaesthesiology (EJA)*, 2008, vol. 25, p. 130.

[83] M. Kodaka, J. W. Johansen, and P. S. Sebel, "The Influence of Gender on Loss of Consciousness with Sevoflurane or Propofol," *Anesth. Analg.*, vol. 101, no. 2, pp. 377–381, Aug. 2005, doi: 10.1213/01.ANE.0000154534.71371.4F.

[84] N. Büttner, B. Schultz, U. Grouven, and A. Schultz, "[EEG-adjusted target-controlled infusion : Propofol target concentration with different doses of remifentanil]," *Anaesthesist*, vol. 59, no. 2, pp. 126–134, Feb. 2010, doi: 10.1007/s00101-009-1666-1.

[85] C. Smith *et al.*, "The interaction of fentanyl on the Cp50 of propofol for loss of consciousness and skin incision.," *Anesthesiology*, vol. 81, no. 4, pp. 820–8; discussion 26A, Oct. 1994.

[86] F. A. Lobo and S. Schraag, "Limitations of anaesthesia depth monitoring," *Curr. Opin. Anaesthesiol.*, vol. 24, no. 6, pp. 657–64, 2011, doi: 10.1097/ACO.0b013e32834c7aba.

[87] A. A. Dahaba, "Different conditions that could result in the bispectral index indicating an incorrect hypnotic state," *Anesth. Analg.*, vol. 101, no. 3, pp. 765–73, 2005, doi: 10.1213/01.ane.0000167269.62966.af.

[88] "Covidien." [Online]. Available: http://www.covidien.com/rms/brands/BIS.

[89] R. R. Nunes, I. M. M. Chaves, J. C. G. de Alencar, S. B. Franco, Y. G. B. R. de Oliveira, and D. G. A. de Menezes, "Bispectral index and other processed parameters of electroencephalogram: an update.," *Rev. Bras. Anestesiol.*, vol. 62, no. 1, pp. 105–17, Jan. , doi: 10.1016/S0034-7094(12)70109-5.

[90] I. J. Rampil, "A primer for EEG signal processing in anesthesia.," *Anesthesiology*, vol. 89, no. 4, pp. 980–1002, Oct. 1998.

[91] J. Dryden, "Preventing memories of surgery," *Washington University in St. Louis*, 2011. [Online].

Available: https://www.youtube.com/watch?v=fHAkVSyOym8. [Accessed: 19-Aug-2011].
[92] J. Lang, “Awakening,” *Atl.*, 2013.
[93] R. Zanner, S. Pilge, E. F. F. Kochs, M. Kreuzer, and G. Schneider, “Time delay of electroencephalogram index calculation: analysis of cerebral state, bispectral, and Narcotrend indices using perioperatively recorded electroencephalographic signals,” *Br. J. Anaesth.*, vol. 103, no. 3, pp. 394–9, Sep. 2009, doi: 10.1093/bja/aep198.
[94] S. Pilge, R. Zanner, G. Schneider, J. Blum, M. Kreuzer, and E. F. Kochs, “Time delay of index calculation: analysis of cerebral state, bispectral, and narcotrend indices,” *Anesthesiology*, vol. 104, no. 3, pp. 488–494, 2006.
[95] A. L. Ferreira, C. S. Nunes, J. Gabriel, and P. Amorim, “The influence of two different drug infusion profiles on the pharmacodynamics model performance,” in *World Congress on Medical Physics and Biomedical Engineering, June 7-12, 2015, Toronto, Canada*, D. A. Jaffray, Ed. Springer International Publishing, 2015, pp. 874–880.
[96] C. F. Minto, T. W. Schnider, T. G. Short, K. M. Gregg, A. Gentilini, and S. L. Shafer, “Response surface model for anesthetic drug interactions.,” *Anesthesiology*, vol. 92, no. 6, pp. 1603–16, Jun. 2000.
[97] J. Bruhn, T. W. Bouillon, L. Radulescu, A. Hoeft, E. Bertaccini, and S. L. Shafer, “Correlation of approximate entropy, bispectral index, and spectral edge frequency 95 (SEF95) with clinical signs of ‘anesthetic depth’ during coadministration of propofol and remifentanil.,” *Anesthesiology*, vol. 98, no. 3, pp. 621–7, Mar. 2003.
[98] J. Shepherd, J. Jones, G. K. Frampton, J. Bryant, L. Baxter, and K. Cooper, “Clinical effectiveness and cost-effectiveness of depth of anaesthesia monitoring (E-Entropy, Bispectral Index and Narcotrend): A systematic review and economic evaluation,” *Health Technol. Assess. (Rockv).*, 2013, doi: 10.3310/hta17340.
[99] P. L. Purdon *et al.*, “The Ageing Brain: Age-dependent changes in the electroencephalogram during propofol and sevoflurane general anaesthesia,” *Br. J. Anaesth.*, vol. 115, pp. i46–i57, Jul. 2015, doi: 10.1093/bja/aev213.
[100] P. S. Myles, D. L. Williams, M. Hendrata, H. Anderson, and A. M. Weeks, “Patient satisfaction after anaesthesia and surgery: Results of a prospective survey of 10,811 patients,” *Br. J. Anaesth.*, 2000, doi: 10.1093/oxfordjournals.bja.a013383.
[101] K. Leslie, M. T. V. Chan, P. S. Myles, A. Forbes, and T. J. McCulloch, “Posttraumatic Stress Disorder in Aware Patients from the B-Aware Trial,” *Anesth. Analg.*, vol. 110, no. 3, pp. 823–828, Mar. 2010, doi: 10.1213/ANE.0b013e3181b8b6ca.
[102] P. S. Myles, K. Leslie, J. McNeil, A. Forbes, and M. T. V Chan, “Bispectral index monitoring to prevent awareness during anaesthesia: the B-Aware randomised controlled trial.,” *Lancet*, vol. 363, no. 9423, pp. 1757–63, May 2004, doi: 10.1016/S0140-6736(04)16300-9.
[103] J. W. Johansen, “Update on bispectral index monitoring.,” *Best Pract. Res. Clin. Anaesthesiol.*, vol. 20, no. 1, pp. 81–99, Mar. 2006.
[104] M. Luginbühl and T. W. Schnider, “Detection of awareness with the bispectral index: two case reports.,” *Anesthesiology*, vol. 96, no. 1, pp. 241–3, Jan. 2002.
[105] K. Leslie, P. S. Myles, A. Forbes, and M. T. V. Chan, “The Effect of Bispectral Index Monitoring on Long-Term Survival in the B-Aware Trial,” *Anesth. Analg.*, vol. 110, no. 3, pp. 816–822, Mar. 2010, doi: 10.1213/ANE.0b013e3181c3bfb2.
[106] M. D. Kertai *et al.*, “Association of Perioperative Risk Factors and Cumulative Duration of Low Bispectral Index with Intermediate-term Mortality after Cardiac Surgery in the B-Unaware Trial,” *Anesthesiology*, vol. 112, no. 5, pp. 1116–1127, May 2010, doi: 10.1097/ALN.0b013e3181d5e0a3.
[107] A. Ferreira, C. Nunes, A. L. Ferreira, R. Tedim, and P. Amorim, “Inter-patient variability and predictive factors of propofol requirements and estimated concentrations for loss of consciousness and recovery,” *J. Neurosurg. Anesthesiol.*, vol. 27, no. 4, pp. 260–261, 2015.
[108] T. Takagi and M. Sugeno, “Fuzzy identification of systems and its applications to modeling and control,” *IEEE Trans. Syst. Man. Cybern.*, vol. SMC-15, no. 1, pp. 116–132, Jan. 1985, doi: 10.1109/TSMC.1985.6313399.
[109] J.-S. R. Jang, “ANFIS: adaptive-network-based fuzzy inference system,” *IEEE Trans. Syst. Man. Cybern.*, vol. 23, no. 3, pp. 665–685, 1993, doi: 10.1109/21.256541.
[110] E. B. Friedman *et al.*, “A conserved behavioral state barrier impedes transitions between anesthetic-induced unconsciousness and wakefulness: evidence for neural inertia.,” *PLoS One*,

vol. 5, no. 7, p. e11903, Jan. 2010, doi: 10.1371/journal.pone.0011903.
[111] J. D. Kenny *et al.*, "Physostigmine and Methylphenidate Induce Distinct Arousal States During Isoflurane General Anesthesia in Rats.," *Anesth. Analg.*, vol. 123, no. 5, pp. 1210–1219, 2016, doi: 10.1213/ANE.0000000000001234.
[112] W. J. Joiner *et al.*, "Genetic and anatomical basis of the barrier separating wakefulness and anesthetic-induced unresponsiveness.," *PLoS Genet.*, vol. 9, no. 9, p. e1003605, Jan. 2013, doi: 10.1371/journal.pgen.1003605.
[113] C. E. Warnaby, J. W. Sleigh, D. Hight, S. Jbabdi, and I. Tracey, "Investigation of Slow-wave Activity Saturation during Surgical Anesthesia Reveals a Signature of Neural Inertia in Humans," *Anesthesiology*, vol. 127, no. 4, pp. 645–657, Oct. 2017, doi: 10.1097/ALN.0000000000001759.
[114] P. O. Sepúlveda *et al.*, "Evidence of hysteresis in propofol pharmacodynamics.," *Anaesthesia*, vol. 73, no. 1, pp. 40–48, Jan. 2018, doi: 10.1111/anae.14009.
[115] P. J. Colin, M. H. Kuizenga, H. E. M. Vereecke, and M. M. R. F. Struys, "Pharmacokinetic Pharmacodynamic Perspective on the Detection of Signs of Neural Inertia in Humans," *Anesthesiology*, vol. 129, no. 2, pp. 373–375, Aug. 2018, doi: 10.1097/ALN.0000000000002287.
[116] W. S. Yew, S. Y. Chong, K. H. Tan, and M. H. Goh, "The effects of intravenous lidocaine on pain during injection of medium- and long-chain triglyceride propofol emulsions.," *Anesth. Analg.*, vol. 100, no. 6, pp. 1693–5, Jun. 2005, doi: 10.1213/01.ANE.0000151718.58709.0B.
[117] D. Memiş, A. Turan, B. Karamanlioğlu, N. Süt, and Z. Pamukçu, "The prevention of pain from injection of rocuronium by ondansetron, lidocaine, tramadol, and fentanyl.," *Anesth. Analg.*, vol. 94, no. 6, pp. 1517–20, table of contents, Jun. 2002.
[118] S. L. Shafer, J. R. Varvel, N. Aziz, and J. C. Scott, "Pharmacokinetics of fentanyl administered by computer-controlled infusion pump.," *Anesthesiology*, vol. 73, no. 6, pp. 1091–102, Dec. 1990.
[119] C. S. Nunes, D. A. Ferreira, L. Antunes, F. Lobo, I. A. Santos, and P. Amorim, "Individual effect-site concentrations of propofol at return of consciousness are related to the concentrations at loss of consciousness and age in neurosurgical patients," *J. Clin. Anesth.*, vol. 21, no. 1, pp. 3–8, 2009, doi: 10.1016/j.jclinane.2008.06.011.
[120] Y. Sun *et al.*, "High throughput modular chambers for rapid evaluation of anesthetic sensitivity.," *BMC Anesthesiol.*, vol. 6, p. 13, Jan. 2006, doi: 10.1186/1471-2253-6-13.
[121] J. B. Glen and M. White, "A comparison of the predictive performance of three pharmacokinetic models for propofol using measured values obtained during target-controlled infusion.," *Anaesthesia*, vol. 69, no. 6, pp. 550–7, Jun. 2014, doi: 10.1111/anae.12631.
[122] J. B. Glen and F. Servin, "Evaluation of the predictive performance of four pharmacokinetic models for propofol," *Br. J. Anaesth.*, vol. 102, no. 5, pp. 626–632, May 2009, doi: 10.1093/bja/aep043.
[123] K. Masui *et al.*, "The performance of compartmental and physiologically based recirculatory pharmacokinetic models for propofol: A comparison using bolus, continuous, and target-controlled infusion data," *Anesth. Analg.*, vol. 111, no. 2, pp. 368–79, 2010, doi: 10.1213/ANE.0b013e3181bdcf5b.
[124] E. Lang, A. Kapila, D. Shlugman, J. F. Hoke, P. S. Sebel, and P. S. Glass, "Reduction of isoflurane minimal alveolar concentration by remifentanil.," *Anesthesiology*, vol. 85, no. 4, pp. 721–8, Oct. 1996.
[125] C. L. Westmoreland, P. S. Sebel, and A. Gropper, "Fentanyl or alfentanil decreases the minimum alveolar anesthetic concentration of isoflurane in surgical patients.," *Anesth. Analg.*, vol. 78, no. 1, pp. 23–8, Jan. 1994.
[126] C. ROSOW, "Anesthetic Drug Interaction: An Overview," *J. Clin. Anesth.*, vol. 9, no. 6, pp. 27S-32S, Sep. 1997, doi: 10.1016/S0952-8180(97)00124-4.
[127] P. S. Glass, M. Bloom, L. Kearse, C. Rosow, P. Sebel, and P. Manberg, "Bispectral analysis measures sedation and memory effects of propofol, midazolam, isoflurane, and alfentanil in healthy volunteers.," *Anesthesiology*, vol. 86, no. 4, pp. 836–47, Apr. 1997.
[128] A. Schultz, M. Siedenberg, U. Grouven, T. Kneif, and B. Schultz, "Comparison of Narcotrend Index, Bispectral Index, spectral and entropy parameters during induction of propofol-remifentanil anaesthesia," *J. Clin. Monit. Comput.*, vol. 22, no. 2, pp. 103–111, Apr. 2008, doi: 10.1007/s10877-008-9111-6.
[129] G. N. Schmidt, P. Bischoff, T. Standl, G. Lankenau, M. Hilbert, and J. Schulte Am Esch, "Comparative evaluation of Narcotrend, Bispectral Index, and classical electroencephalographic variables during induction, maintenance, and emergence of a propofol/remifentanil anesthesia.,"

Anesth. Analg., vol. 98, no. 5, pp. 1346–53, table of contents, May 2004.
[130] R. H. Sandin, G. Enlund, P. Samuelsson, and C. Lennmarken, "Awareness during anaesthesia: a prospective case study," *Lancet*, vol. 9, no. 9205, pp. 707–11, Feb. 2000, doi: 10.1016/S0140-6736(99)11010-9.
[131] N. Moerman, B. Bonke, and J. Oosting, "Awareness and recall during general anesthesia. Facts and feelings.," *Anesthesiology*, vol. 79, no. 3, pp. 454–64, Sep. 1993.
[132] R. J. Pollard, J. P. Coyle, R. L. Gilbert, and J. E. Beck, "Intraoperative awareness in a regional medical system: a review of 3 years' data.," *Anesthesiology*, vol. 106, no. 2, pp. 269–74, Feb. 2007.
[133] A. T. Phillips, S. Deiner, H. Mo Lin, E. Andreopoulos, J. Silverstein, and M. A. Levin, "Propofol Use in the Elderly Population: Prevalence of Overdose and Association With 30-Day Mortality," *Clin. Ther.*, vol. 37, no. 12, pp. 2676–2685, Dec. 2015, doi: 10.1016/j.clinthera.2015.10.005.
[134] B. Babadi and E. N. Brown, "A Review of Multitaper Spectral Analysis," *IEEE Trans. Biomed. Eng.*, vol. 61, no. 5, pp. 1555–1564, May 2014, doi: 10.1109/TBME.2014.2311996.
[135] J. M. Alho, *Book Review: The Analysis of Time Series – An Introduction*. London: Chapman and Hall, 1997.
[136] H. Bokil, P. Andrews, J. E. Kulkarni, S. Mehta, and P. P. Mitra, "Chronux: A platform for analyzing neural signals," *J. Neurosci. Methods*, vol. 192, no. 1, pp. 146–151, Sep. 2010, doi: 10.1016/J.JNEUMETH.2010.06.020.
[137] Food and Drug Administration, "Dripivan (propofol) injectable emulsion," *451094H/Revised*, 2017. .
[138] D. N. Stokes and P. Hutton, "Rate-dependent induction phenomena with propofol: implications for the relative potency of intravenous anesthetics.," *Anesth. Analg.*, vol. 72, no. 5, pp. 578–83, May 1991.
[139] R. H. Sandin, G. Enlund, P. Samuelsson, and C. Lennmarken, "Awareness during anaesthesia: a prospective case study," *J. Clin. Anesth*, vol. 9, no. 6, pp. 27S-32S, 1997.
[140] A. L. Ferreira, J. G. Mendes, C. S. Nunes, and P. Amorim, "Evaluation of Bispectral Index time delay in response to anesthesia induction: an observational study," *Brazilian J. Anesthesiol. (English Ed.*, vol. 69, no. 4, pp. 377–382, May 2019, doi: https://doi.org/10.1016/j.bjane.2019.04.006.
[141] O. Ortolani *et al.*, "EEG signal processing in anaesthesia. Use of a neural network technique for monitoring depth of anaesthesia," *Br. J. Anaesth.*, vol. 88, pp. 644–648, 2002, doi: 10.1093/bja/88.5.644.
[142] G. J. A. Jiang *et al.*, "Sample Entropy Analysis of EEG Signals via Artificial Neural Networks to Model Patients' Consciousness Level Based on Anesthesiologists Experience," *Biomed Res. Int.*, vol. 2015, p. 343478, Feb. 2015, doi: 10.1155/2015/343478.
[143] Y. Gu, Z. Liang, and S. Hagihira, "Use of Multiple EEG Features and Artificial Neural Network to Monitor the Depth of Anesthesia," *Sensors*, vol. 19, no. 11, p. 2499, May 2019, doi: 10.3390/s19112499.
[144] C. N. Sessler *et al.*, "The Richmond Agitation–Sedation Scale," *Am. J. Respir. Crit. Care Med.*, vol. 166, no. 10, pp. 1338–1344, Nov. 2002, doi: 10.1164/rccm.2107138.
[145] V. Nair and G. E. Hinton, "Rectified linear units improve restricted boltzmann machines," in *Proceedings of the 27th international conference on machine learning (ICLML)*, 2010, pp. 807–814.
[146] M. Z. Alom *et al.*, "A State-of-the-Art Survey on Deep Learning Theory and Architectures," *Electronics*, vol. 8, no. 3, p. 292, 2019.
[147] I. Goodfellow, Y. Bengio, and A. Courville, *Deep learning*. MIT Press, 2016.
[148] Python Software Foundation, "Python: A dynamic, open source programming language." 2015.
[149] A. Paszke *et al.*, "Automatic differentiation in PyTorch," in *NIPS 2017 Workshop Autodiff*, 2017.
[150] S. Ioffe and C. Szegedy, "Batch normalization: Accelerating deep network training by reducing internal covariate shif," in *International Conference on Machine Learning*, 2015, pp. 448–456.
[151] D. P. Kingma and J. L. Ba, "Adam: A Method for Stochastic Optimization," in *3rd International Conference for Learning Representations*, 2015.
[152] M. Sokolova and G. Lapalme, "A systematic analysis of performance measures for classification tasks," *Inf. Process. Manag.*, vol. 45, no. 4, pp. 427–437, Jul. 2009, doi: 10.1016/J.IPM.2009.03.002.
[153] P. Gambus and S. L. Shafer, "Artificial Intelligence for Everyone," *Anesthesiology*, vol. 128, no.

3, pp. 431–433, Mar. 2018, doi: 10.1097/ALN.0000000000001984.
[154] Q. Liu, L. Ma, S.-Z. Fan, M. F. Abbod, and J.-S. Shieh, “Sample entropy analysis for the estimating depth of anaesthesia through human EEG signal at different levels of unconsciousness during surgeries,” *PeerJ*, vol. 6, p. e4817, May 2018, doi: 10.7717/peerj.4817.
[155] R. Shalbaf, H. Behnam, J. W. Sleigh, A. Steyn-Ross, and L. J. Voss, “Monitoring the depth of anesthesia using entropy features and an artificial neural network,” *J. Neurosci. Methods*, no. 19, pp. 2499-, 2013, doi: 10.1016/j.jneumeth.2013.03.008.
[156] A. Shalbaf, M. Saffar, J. W. Sleigh, and R. Shalbaf, “Monitoring the depth of anesthesia using a new adaptive neurofuzzy system,” *IEEE J. Biomed. Heal. Informatics*, vol. 22, pp. 671–677, 2018, doi: 10.1109/JBHI.2017.2709841.
[157] C. Guo, J. Yu, L. Wu, Y. Liu, C. Jia, and Y. Xie, “Analysis and feature extraction of EEG signals induced by anesthesia monitoring based on wavelet transform,” *IEEE Access*, vol. 7, pp. 41565–41575, 2019, doi: 10.1109/ACCESS.2019.2907794.
[158] J. Bruhn, P. S. Myles, R. Sneyd, and M. M. R. F. Struys, “Depth of anaesthesia monitoring: what’s available, what’s validated and what’s next?,” *Br. J. Anaesth.*, vol. 97, no. 1, pp. 85–94, Jul. 2006, doi: 10.1093/bja/ael120.
[159] C. Szegedy *et al.*, “Going Deeper with Convolutions,” *CoRR*, vol. abs/1409.4, 2014.
[160] T. D. Caputo *et al.*, “Evaluation of the SEDline to improve the safety and efficiency of conscious sedation.,” *Proc. (Bayl. Univ. Med. Cent).*, vol. 24, no. 3, pp. 200–4, Jul. 2011, doi: 10.1080/08998280.2011.11928715.
[161] B. Goudra, P. M. Singh, G. Gouda, A. Borle, A. Carlin, and A. Yadwad, “Propofol and non-propofol based sedation for outpatient colonoscopy-prospective comparison of depth of sedation using an EEG based SEDLine monitor.,” *J. Clin. Monit. Comput.*, vol. 30, no. 5, pp. 551–7, Oct. 2016, doi: 10.1007/s10877-015-9769-5.
[162] M. A. Claeys, E. Gepts, and F. Camu, “Haemodynamic changes during anaesthesia induced and maintained with propofol.,” *Br. J. Anaesth.*, vol. 60, no. 1, pp. 3–9, Jan. 1988.
[163] G. E. Larijani, I. Gratz, M. Afshar, and A. G. Jacobi, “Clinical pharmacology of propofol: an intravenous anesthetic agent.,” *DICP*, vol. 23, no. 10, pp. 743–9, Oct. 1989.
[164] C. E. Warnaby *et al.*, “Anesthesia-induced Suppression of Human Dorsal Anterior Insula Responsivity at Loss of Volitional Behavioral Response.,” *Anesthesiology*, vol. 124, no. 4, pp. 766–78, Apr. 2016, doi: 10.1097/ALN.0000000000001027.
[165] L. Bosch, J. Fernández-Candil, A. León, and P. L. Gambús, “Influencia de la anestesia general sobre el tronco encefálico,” *Rev. Esp. Anestesiol. Reanim.*, vol. 64, no. 3, pp. 157–167, Mar. 2017, doi: 10.1016/j.redar.2016.09.005.
[166] J. J. Pellegrini, A. K. Horn, and C. Evinger, “The trigeminally evoked blink reflex. I. Neuronal circuits.,” *Exp. brain Res.*, vol. 107, no. 2, pp. 166–80, 1995, doi: 10.1007/bf00230039.
[167] B. Shahani, “The human blink reflex,” *J. Neurol. Neurosurg. Psychiatry*, vol. 33, no. 6, pp. 792–800, Dec. 1970.
[168] D. C. Preston and B. E. Shapiro, *Electromyography and neuromuscular disorders : clinical-electrophysiological correlations*, 3rd ed. Elsevier Saunders, 2013.
[169] H. J. Lee and J. A. Delisa, *Manual of Nerve Conduction Study and Surface Anatomy for Needle Electromyography*, 4th ed. Lippincott Williams & Wilkins, 2005.
[170] B. E. Smith, “Cranial Reflexes and Related Techniques,” in *Clinical Neurophysiology*, Third edit., J. R. Daube and D. I. Rubin, Eds. Oxford, 2009, pp. 529–542.
[171] J. Mourisse, J. Lerou, M. Zwarts, and L. Booij, “Electromyographic assessment of blink reflexes correlates with a clinical scale of depth of sedation/anaesthesia and BIS during propofol administration,” *Acta Anaesthesiol. Scand.*, vol. 48, no. 9, pp. 1174–1179, Oct. 2004, doi: 10.1111/j.1399-6576.2004.00485.x.
[172] J. B. B. Brooks, M. R. Jardim, R. M. Papais-Alvarenga, and Y. D. Fragoso, “Time Parameters of the Blink Reflex in Normal Subjects,” *Neurophysiology*, vol. 46, no. 3, pp. 221–224, Jun. 2014, doi: 10.1007/s11062-014-9432-7.
[173] J.-K. Yoo, J. Cho, and D. Kim, “Utilization of Averaging Process of Blink Reflex to Improve Diagnosis of Facial Nerve Palsy,” *J. Exp. Biomed. Sci.*, vol. 18, no. 4, pp. 391–398, 2012.
[174] J. Mourisse, J. Lerou, M. Struys, M. Zwarts, and L. Booij, “Multi-level approach to anaesthetic effects produced by sevoflurane or propofol in humans: 1. BIS and blink reflex,” *Br. J. Anaesth.*, vol. 98, no. 6, pp. 737–745, May 2007, doi: 10.1093/bja/aem104.
[175] B. W. Ongerboer de Visser, “Anatomical and functional organization of reflexes involving the

trigeminal system in man: jaw reflex, blink reflex, corneal reflex, and exteroceptive suppression.," *Adv. Neurol.*, vol. 39, pp. 727–38, 1983.
[176] G. Cruccu, S. Ferracuti, M. G. Leardi, A. Fabbri, and M. Manfredi, "Nociceptive quality of the orbicularis oculi reflexes as evaluated by distinct opiate- and benzodiazepine-induced changes in man.," *Brain Res.*, vol. 556, no. 2, pp. 209–17, Aug. 1991.
[177] E. N. Brown, P. L. Purdon, and C. J. Van Dort, "General Anesthesia and Altered States of Arousal: A Systems Neuroscience Analysis," *Annu. Rev. Neurosci.*, vol. 34, no. 1, pp. 601–628, Jul. 2011, doi: 10.1146/annurev-neuro-060909-153200.
[178] W. B. Mendelson, "Neuropharmacology of sleep induction by benzodiazepines.," *Crit. Rev. Neurobiol.*, vol. 6, no. 4, pp. 221–32, 1992.
[179] G. Haeseler *et al.*, "Propofol blocks human skeletal muscle sodium channels in a voltage-dependent manner.," *Anesth. Analg.*, vol. 92, no. 5, pp. 1192–8, May 2001.
[180] T. W. Bouillon *et al.*, "Pharmacodynamic interaction between propofol and remifentanil regarding hypnosis, tolerance of laryngoscopy, bispectral index, and electroencephalographic approximate entropy.," *Anesthesiology*, vol. 100, no. 6, pp. 1353–72, Jun. 2004.
[181] J. Posner, C. Saper, N. Schiff, and F. Plum, *Plum and Posner's diagnosis of stupor and coma*. New York: Oxford University Press, 2007.
[182] S. P *et al.*, "Differential Frontal Alpha Oscillations and Mechanisms Underlying Loss of Consciousness: A Comparison Between Slow and Fast Propofol Infusion Rates," *Anaesthesia*, vol. 75, no. 2, 2020, doi: 10.1111/ANAE.14885.
[183] H. A. Javaid, N. Rashid, M. I. Tiwana, and M. W. Anwar, "Comparative Analysis of EMG Signal Features in Time-domain and Frequency-domain using MYO Gesture Control," in *Proceedings of the 2018 4th International Conference on Mechatronics and Robotics Engineering*, 2018, pp. 157–172.
[184] J. Kimura, *Electrodiagnosis in Diseases of Nerve and Muscle: Principles and Practice*, 4th ed. New York: Oxford University Press, 2013.
[185] L. A. Medvedeva, A. V. Syrovegin, G. N. Avakyan, A. V. Gnezdilov, and O. I. Zagorulko, "Methods for studying the blink reflex and its normative parameters," *Neurosci. Behav. Physiol.*, vol. 42, no. 1, pp. 1–7, 2012, doi: 10.1007/s11055-011-9524-4.
[186] P. Schwingenschuh *et al.*, "The blink reflex recovery cycle differs between essential and presumed psychogenic blepharospasm.," *Neurology*, vol. 76, no. 7, pp. 610–4, Feb. 2011, doi: 10.1212/WNL.0b013e31820c3074.
[187] A. Berardelli, N. Accornero, G. Cruccu, F. Fabiano, V. Guerrisi, and M. Manfredi, "The orbicularis oculi response after hemispheral damage.," *J. Neurol. Neurosurg. Psychiatry*, vol. 46, no. 9, pp. 837–43, Sep. 1983.
[188] R. Agostino, A. Berardelli, G. Cruccu, F. Stocchi, and M. Manfredi, "Corneal and blink reflexes in Parkinson's disease with 'on-off' fluctuations," *Mov. Disord.*, vol. 2, no. 4, pp. 227–235, 1987, doi: 10.1002/mds.870020401.
[189] J. Mourisse, W. Gerrits, J. Lerou, J. van Egmond, M. J. Zwarts, and L. Booij, "Electromyographic assessment of blink and corneal reflexes during midazolam administration: useful methods for assessing depth of anesthesia?," *Acta Anaesthesiol. Scand.*, vol. 47, no. 5, pp. 593–600, May 2003.
[190] P. O. Sepúlveda *et al.*, "Evidence of hysteresis in propofol pharmacodynamics," *Anaesthesia*, vol. 73, no. 1, pp. 40–48, Sep. 2018, doi: 10.1111/anae.14009.
[191] A. Castro, N. Bressan, F. Lobo, C. Nunes, and P. Amorim, "The higher the propofol concentration needed for loss of consciousness the larger its difference to the concentrations required at maintenance, using TCI and BIS guided anesthesia," *Eur. J. Anaesthesiol.*, vol. 25, no. Sup 44, p. 150, 2008, doi: 10.1097/00003643-200805001-00480.
[192] J. E. Mandel, "Safe Driving on the Pharmacokinetic Highway.," *Anesth. Analg.*, vol. 125, no. 4, pp. 1100–1101, 2017, doi: 10.1213/ANE.0000000000002382.
[193] A. L. Ferreira, C. Nunes, J. G. Mendes, and P. Amorim, "¿Contamos actualmente con un método fiable para detectar el momento de pérdida de consciencia durante la inducción de la anestesia?," *Rev. Esp. Anestesiol. Reanim.*, vol. 66, no. 2, pp. 93–103, Feb. 2019, doi: 10.1016/j.redar.2018.06.008.
[194] A. Esteban, "A neurophysiological approach to brainstem reflexes. Blink reflex," *Neurophysiol. Clin. Neurophysiol.*, vol. 29, no. 1, pp. 7–38, Feb. 1999, doi: 10.1016/S0987-7053(99)80039-2.
[195] A. Phinyomark, P. Phukpattaranont, and C. Limsakul, "Feature reduction and selection for EMG

signal classification," *Expert Syst. Appl.*, vol. 39, no. 8, pp. 7420–7431, 2012.
[196] T. Inouye *et al.*, "Quantification of EEG irregularity by use of the entropy of the power spectrum," *Electroencephalogr. Clin. Neurophysiol.*, vol. 79, no. 3, pp. 204–210, 1991, doi: 10.1016/0013-4694(91)90138-T.
[197] D. Jordan, M. Steiner, E. F. Kochs, and G. Schneider, "A program for computing the prediction probability and the related receiver operating characteristic graph," *Anesth. Analg.*, vol. 111, no. 6, pp. 1416–21, 2010, doi: 10.1213/ANE.0b013e3181fb919e.
[198] W. D. Smith, R. C. Dutton, and N. T. Smith, "Measuring the performance of anesthetic depth indicators," *Anesthesiology*, vol. 84, no. 1, pp. 38–51, 1996, doi: 10.1097/00000542-199601000-00005.
[199] J. Hosmer, D.W., S. Lemeshow, and R. X. Sturdivant, *Logistic Regression Models for Multinomial and ordinal Outcomes*. In Applied Logistic Regression, 2013.
[200] S. R, B. H, S. JW, S.-R. A, and V. LJ, "Monitoring the depth of anesthesia using entropy features and an artificial neural network," *J Neurosci Methods*, vol. 218, no. 1, pp. 17–24, 2013.
[201] A. Vakkuri *et al.*, "Time-frequency balanced spectral entropy as a measure of anesthetic drug effect in central nervous system during sevoflurane, propofol, and thiopental anesthesia," *Acta Anaesthesiol. Scand.*, vol. 48, no. 2, pp. 145–53, 2004, doi: 10.1111/j.0001-5172.2004.00323.x.
[202] P. A., T. S., H. H., P. P., and L. C., "The usefulness of mean and median frequencies in electromyography analysis," in *Computational Intelligence in Electromyography Analysis - A Perspective on Current Applications and Future Challenges*, N. G.R., Ed. London: InTech, 2012, pp. 195–220.
[203] S. Thongpanja, A. Phinyomark, P. Phukpattaranont, C. Limsakul, and K. Hong, "Mean and Median Frequency of EMG Signal to Determine Muscle Force based on Time- dependent Power Spectrum," *Elektron. Ir Elektrotechnika*, vol. 19, p. 51.56, 2013.
[204] J. M. Gonzalez-Cava, J. A. Reboso, J. L. Calvo-Rolle, and J. A. Mendez-Perez, "Adaptive drug interaction model to predict depth of anesthesia in the operating room," *Biomed. Signal Process. Control*, vol. 59, p. 101931, 2020, doi: https://doi.org/10.1016/j.bspc.2020.101931.

Appendix A

Questionnaire: how much and how to administer propofol in the induction phase of general anesthesia and how to evaluate its effects

This survey focuses on how anesthesiologists administer propofol in the induction phase of general anesthesia. The survey is being carried out under my doctoral project in Biomedical Engineering from FEUP (Faculty of Engineering of the University of Oporto, Portugal) entitled "Advanced evaluation consciousness in anesthesia". The following questionnaire is composed of ten simple questions, it takes about five minutes to complete, it is anonymous, and it will be used exclusively for research purposes. It is not a test, there are no right or wrong answers, but each question can only have one answer. Your support is very important for my project. I ask you to be truthful in your answers. Your answers should be provided based on your clinical experience.

Scenario

A male patient, 50 years old, 60 kg, 1.60 m, ASA I, without premedication, is ready to undergo induction of general anesthesia and tracheal intubation to perform a cholecystectomy by laparotomy. Fentanyl, 0.15mg, was administered, followed three minutes later by 1% propofol delivered manually with a 20-cc syringe. The anesthesiologist is at the head of the patient, pre-oxygenating, monitoring and instructing the nurse administering the drugs through an IV line inserted in the back of the patient's hand. Standard monitoring is ASA and BIS.

1. What is your experience as an anesthesiologist?

    □ Intern

    □ Expert for less than 5 years

    □ Expert for more than 5 years

2. In the scenario above, what dosage of propofol (in mg) would you administer for induction?

    _____

3. In your clinical practice, for the dosage chosen, how fast (in ml/h) is the administration of propofol (1% by a 20cc syringe administered by a nurse) typically performed? (Choose the value that appears most approximate to the one occurring in your practice)

    □ 120 ml/h

    □ 200 ml/h

    □ 600 ml/h

- 1200 ml/h
- 1400 ml/h or more

4. When performing the induction, administering propofol in the dosage and speed that you normally use, how do you proceed:
   - You evaluate the state of consciousness every 10 seconds and instruct the nurse to administrate propofol and stop only when the patient loses consciousness.
   - You instruct the nurse to administer a dosage that seems appropriate and evaluate if the patient has lost consciousness, administering an additional dosage if the patient still remains conscious.
   - You instruct the nurse to administer a dosage that seems appropriate and wait at least 60 seconds before assessing if the patient has lost consciousness or if a further dosage is needed.
5. In the scenario above, during the induction of anesthesia with propofol, which method do you use to assess the loss of consciousness (choose only one, the one you consider most important):
   - By asking the patient to count (up to ten or twenty, for example) and considering that loss of consciousness occurs when he/she stops counting.
   - By relying on the BIS value.
   - By the loss of the eyelid reflex.
   - By observing the absence of eye opening or movement in response to a call by his/her name.
   - By assessing the loss of muscle tone (raising the arm of the patient and assess whether it ceases to resist the fall).

- □ By the absence of any movement when tapping on the forehead or shaking the shoulder.
- □ By the absence of reaction (no movement) in response to a pinch in the shoulder area.

6. When you use monitoring with BIS and the BIS starts decreasing during induction as a consequence of the propofol administration, which is the value below which you believe one can tell when patients, on average, lose consciousness?
   - □ I never use monitoring with BIS
   - □ 90
   - □ 85
   - □ 80
   - □ 75
   - □ 70
   - □ 60
7. When you use TCI of propofol with the Schnider model, how do you perform induction in most cases?
   - □ I never use TCI
   - □ I never use the Schnider model
   - □ TCI view mode
   - □ TCI with a predetermined brain target concentration (e.g. 4ug/ml)
   - □ TCI without a predetermined brain target, starting with a low value and increasing it until the patient loses consciousness
   - □ TCI with a predetermined plasma target (e.g. 4ug/ml)
   - □ TCI without a predetermined plasma target starting with a low value and increasing it until the patient loses consciousness

8. During induction, when you stop administrating propofol, overshooting occurs, that is, the maximum brain concentration achieved exceeds the concentration that occurs when the administration has stopped. Considering this patient and the dosage and rate of administration selected in the previous answers, what is your estimate of the magnitude of the overshooting?

    - Less than 20%
    - 20% to 40%
    - 40% to 60%
    - 60% to 80%
    - More than 80%

9. For this patient, if one performs the induction with 3µg/kg of fentanyl and propofol as a 100mg bolus administered within 30 seconds, how long after the end of the injection will the propofol brain concentration achieve its maximum?

    - 5 Seconds
    - 15 Seconds
    - 30 Seconds
    - 60 Seconds
    - 90 Seconds or more

10. During induction of anesthesia in an ASA I, 50 years old, 60 kg and 1.60m patient how often do you measure the blood pressure (non-invasively)?

    - Continuously
    - Every minute
    - Every 2.5 minutes
    - Every 3 minutes
    - Every 5 minutes

Other observations:

_____

_____

Appendix B

B_1 Clinical Protocol – New scheme for individualizing propofol induction and maintenance of general anesthesia

Hospital Geral de Santo António centro hospitalar do Porto

Protocolo Clínico

NOVO ESQUEMA PARA INDIVIDUALIZAÇÃO DE PROPOFOL NA INDUÇÃO E MANUTENÇÃO DA ANESTESIA GERAL

- **Introdução e Objectivos**

A anestesia geral caracteriza-se essencialmente pela perda de consciência e compreende uma fase inicial breve de indução, uma fase mais longa de manutenção e por fim, a recuperação. A indução da anestesia implica essencialmente produzir inconsciência, através da administração de um hipnótico, sendo o propofol o mais frequentemente usado. A perda de consciência (*Loss Of Consciousness* – LOC) é avaliada por sinais clínicos, tradicionalmente pela ausência de abertura dos olhos quando se chama pelo doente ao mesmo tempo que se bate na testa com vigor. Atualmente, o controlo do estado adequado de hipnose/inconsciência é realizado através da monitorização do índice biespectral (BIS) do electroencefalograma (EEG). O BIS deve ser mantido entre 40 e 60 numa escala adimensional em que 100 corresponde à pessoa desperta e 0 à ausência de atividade elétrica cerebral.

Na técnica de TIVA (*Total Intravenous Anesthesia*), muito usada, a manutenção da hipnose durante a anestesia é feita com infusão contínua de propofol. Depois da dose de propofol destinada a produzir inconsciência, segue-se uma perfusão contínua do mesmo fármaco. É bem conhecido que o propofol tem efeitos laterais importantes, nomeadamente hemodinâmicos, causando vasodilatação periférica e diminuição do débito cardíaco e, consequentemente, hipotensão arterial [1,2]. A tensão arterial verificada após a administração do propofol é normalmente 17%-27% inferior ao seu valor basal [3]. Estes efeitos são mais marcados e mais indesejáveis nos doentes idosos ou com menor reserva cardiovascular ou hipovolémicos. Os efeitos laterais do propofol são tanto maiores quanto as concentrações do fármaco, possivelmente ao nível plasmático e cerebral [3]. Por outro lado há muitas vezes necessidade de tratar a hipotensão com fármacos vasoativos e com fluidos para evitar a má perfusão de orgãos nobres, nomeadamente quando já há doença isquémica cardíaca, renal ou cerebral prévia que aumenta esse risco. Como estes efeitos laterais são importantes e temidos, existe uma grande preocupação em administrar a dose adequada de propofol, isto é a mínima dose capaz de produzir e de manter a perda de consciência.

Modernamente, na anestesia endovenosa, administra-se propofol utilizando sistemas TCI (*Target Controlled Infusion*) ou infusão guiada pelo alvo, sendo o alvo a concentração plasmática ou cerebral pretendida [4,5]. A farmacocinética das drogas anestésicas pode ser explicada por modelos matemáticos que têm um compartimento central e um ou dois compartimentos periféricos. Estes compartimentos não correspondem directamente a regiões anatómicas ou fisiológicas. Os sistemas TCI consistem em seringas perfusoras controladas por um computador que incorpora este tipo de modelos farmacocinéticos, e efectuam simulações para prever ao longo do tempo, o curso da concentração plasmática e o efeito do anestésico no local alvo [6]. Para o propofol os modelos mais usados são os de Schnider e de Marsh. A TCI

associada à monitorização do nível da anestesia por índices derivados do EEG permite controlar melhor a anestesia e usar doses mais adequadas de propofol.

Todavia, a TCI é um método caro que implica seringas especiais e não está disponível na maioria dos blocos operatórios, nomeadamente nos países com menos recursos. Para além disso, a sua utilização implica o manuseio do conceito de concentrações plasmáticas e ou cerebrais calculadas (não medidas) e a compreensão das relações entre estas, conceitos que são estranhos á maioria dos anestesiologistas e algo difíceis de incorporar na prática clínica. Roberts e seus colaboradores desenvolveram um esquema para administração de propofol usando uma seringa elétrica convencional sem TCI que permite obter uma concentração plasmática estável de 3ug/ml. Estes autores utilizaram doseamentos plasmáticos e um modelo farmacocinético. O esquema de Roberts consiste numa dose de indução de 1 mg/Kg, seguida imediatamente por uma infusão de 10 mg/Kg/hora durante 10 minutos, 8 mg/Kg/hora nos 10 minutos seguintes e 6 mg/Kg/hora durante o resto da cirurgia [7]. Este esquema revela-se útil, mas tem o problema da dose de indução ser fixa e não ter em conta a enorme variabilidade individual nas necessidades de propofol para provocar LOC (2 a 7 ug/ml) [8]. Quando se usa um sistema TCI subsiste o problema de administrar a dose adequada a cada doente durante a indução. Iniciar TCI definindo como alvo a concentração média com que os doentes perdem consciência, cerca de 3,5ug/ml, resultará numa concentração insuficiente ou excessiva em muitos doentes.

Quando se administra propofol na forma de bólus, usam-se doses por kg de peso recomendadas e o propofol é por regra administrado numa injecção manual habitualmente realizada numa velocidade entre 900 e 1200 ml/h. Apesar de os anestesistas em geral acharem que esta velocidade é adequada e interromperem a administração do bólus quando o doente perde consciência, na realidade estas velocidades de administração do bolus resultam num over-shooting de cerca de 100% na concentração cerebral de propofol necessária para produzir inconsciência devido ao fenómeno de histerese (atraso entre o pico de concentração plasmática e o pico de concentração cerebral) [6]. Uma forma de contornar este problema consiste em iniciar a anestesia com propofol com uma infusão lenta até que ocorra inconsciência. Nesse momento suspende-se a administração, mas a concentração cerebral ainda continua a aumentar, devido ao referido fenómeno de histerese [6]. Acontece que quando se administra um fármaco, nomeadamente através de uma injeção endovenosa lenta, ocorre uma subida progressiva da concentração plasmática acompanhada, embora com um considerável atraso no tempo, de uma subida da concentração no local efeito (cérebro, no caso do propofol). O atraso na concentração cerebral de propofol em relação à plasmática é de cerca de 90 segundos. Desta forma, quando se interrompe de modo abrupto a infusão de propofol no momento em que ocorre LOC, a concentração plasmática começa de imediato a decrescer, mas a cerebral continuará a subir porque a concentração plasmática permanecerá durante algum tempo acima da cerebral até que as concentrações se equilibrem. Assim, sempre que se cessa a administração do fármaco (no momento de LOC), a sua concentração no local de efeito continua a subir por algum tempo. Quanto maior a velocidade de administração, maior a diferença entre as concentrações plasmática e cerebral no momento em que se cessa a administração e maior o *over-shooting* da concentração cerebral, como se

pode ver na figura 1. O *over-shooting* corresponde à diferença entre o pico de concentração cerebral e a concentração cerebral com que o paciente perdeu a consciência.

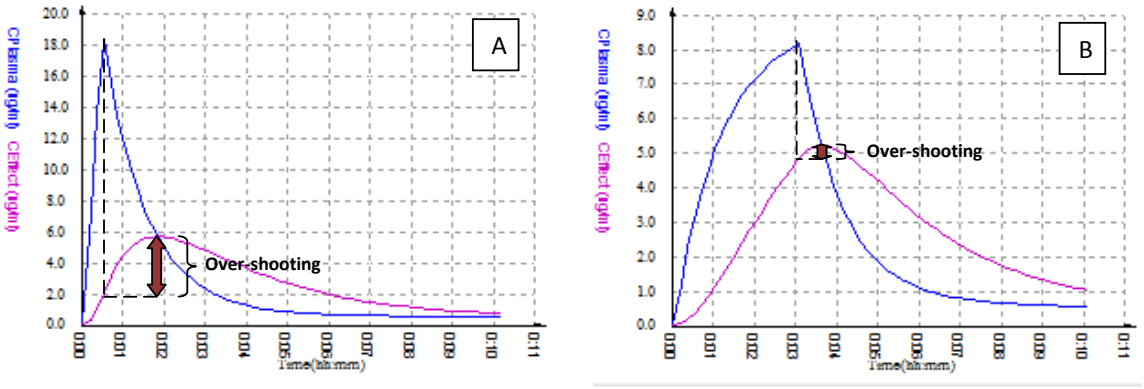


Figura 1. Relação entre as concentrações plasmática e cerebral (mg/ml), em função do tempo (min), para diferentes velocidades de infusão do fármaco propofol: A) Infusão de propofol a 1200ml/h com LOC e paragem de infusão aos 30 segundos. B) Infusão de propofol a 200ml/h com LOC e paragem de infusão aos 180 segundos.

Para além da histerese, que se minimiza através de uma velocidade de indução lenta, há que ter em conta um outro fenómeno importante que afeta a estabilidade do paciente e que é o facto de a concentração necessária para a perda de consciência ser superior à que é necessária para manter inconsciência. No passado, estudamos este fenómeno e desenvolvemos um método para a indução que inclui uma fórmula que indica qual a redução na concentração de propofol que deve ser aplicada para a manutenção adequada. Tal método implica todavia a utilização de um sistema TCI.

Para além da histerese e do over-shooting, que se minimiza através de uma velocidade de indução lenta, há que ter em conta um outro fenómeno importante que afeta a estabilidade do paciente e que é o facto de a concentração necessária para a perda de consciência ser superior à que é necessária para manter inconsciência. No passado estudamos este fenómeno e desenvolvemos um método para a indução que introduziu uma fórmula que indica qual a redução na concentração de propofol que deve ser aplicada para a manutenção adequada nos minutos iniciais após LOC [8]. Esta fórmula tem sido utilizada com sucesso na prática clínica diária e foi também utilizada num estudo clínico que recebeu a aprovação do DEFI e do CA do CHP. Todavia, este método implica a utilização de um sistema TCI e o domínio do conceito de concentrações calculadas.

Conscientes da necessidade e interesse de desenvolver um sistema de administração de propofol mais simples do que um sistema TCI e que permita a individualização da dose necessária para LOC e para manutenção de LOC nos minutos seguintes, concebemos, em 2013, um esquema já apresentado numa comunicação científica. Tal esquema foi feito a partir de dados recolhidos no estudo atrás referido [9].

Este esquema inicia a indução da anestesia com propofol infundido a uma velocidade baseada apenas no peso do doente (a 3,3ml/kg/h) e propõe a velocidade de infusão de propofol após LOC calculada de modo individualizado para cada paciente em função, apenas, da quantidade de propofol, em ml, necessária para produzir LOC. Esta infusão é iniciada 170 segundos após LOC. Assim, num doente de 60 kg, o novo esquema inicia a infusão de propofol (1%) a 198ml/h; se o doente perder a consciência após a administração de, por hipótese, 90 mg, o novo esquema propõe o início de propofol 170 segundos após LOC a uma velocidade de 59ml/h.

Através de cálculos realizados num computador, comparamos este nosso novo esquema, no que respeita às concentrações cerebrais calculadas, com o de Roberts e com a utilização de TCI, e obtivemos resultados que sugerem que pode ser vantajoso [9]. A análise do novo esquema também revela que se adequa apenas aos primeiros minutos após LOC (foi para isso que foi desenvolvido) e que a manter-se o ritmo de infusão calculado a concentração de propofol tenderia a aumentar. Este esquema tem que ser melhorado, requerendo provavelmente reduções na velocidade de administração de propofol ao longo do tempo tal como acontece com o esquema de Roberts.

Acresce ainda que este esquema foi desenvolvido utilizando dados de um estudo clinico [10] no qual os doentes começavam por receber propofol sem a administração prévia de um opióide, iniciando remifentanil depois de LOC. O esquema que pretendemos agora desenvolver destina-se a utilizadores que não dispõem de TCI. O remifentanil é muito caro sendo provável que esses utilizadores também não disponham deste fármaco. Assim sendo, propomo-nos realizar um estudo em condições que mimetizem um cenário simplificado de anestesia total intravenosa. Tal cenário consiste na utilização de fentanil por bólus precedendo o propofol, seguido de propofol em infusão através de seringa perfusora eléctrica sem sistema TCI ou seja, sem incorporar modelos farmacocinéticos nem requerer a utilização de concentrações plasmáticas ou cerebrais.

Admitimos que este novo esquema possa permitir o desenvolvimento de um novo dispositivo médico consistindo numa seringa infusora eléctrica muito simples que tenha um menu que permita o *input* do valor do peso do doente e do momento de LOC, para a partir daí infundir propofol numa dose individualizada e adequada. Pensamos que a utilidade clínica deste dispositivo seria grande e que se poderia traduzir numa atenuação dos efeitos laterais dos anestésicos e num aumento da segurança da anestesia.

Com o presente estudo pretendemos num primeira fase desenvolver um novo esquema, baseado num novo algoritmo, para a administração de propofol para indução e manutenção de anestesia sem recurso a modelos farmacocinéticos ou TCI, que incorpore a capacidade de individualizar a dose de propofol adequada para cada indivíduo durante a indução e calcule a dose adequada para a manutenção da anestesia nos 30 minutos iniciais de modo a que o BIS esteja entre 40 e 60. Para isso serão utilizados dados obtidos em 40 doentes anestesiados de acordo com um protocolo descrito na metodologia.

Numa segunda fase pretende-se validar o novo esquema. Para tal propomo-nos proceder à indução e manutenção nos 30 minutos iniciais da anestesia infundindo propofol de acordo com o novo esquema, avaliando se resulta na obtenção de valores de BIS entre 40 e 60. Tal será realizado em 30 doentes.

Os indicadores a medir serão a pressão arterial, o índice BIS e a quantidade de propofol administrada.

Será ainda realizada uma determinação da concentração plasmática de propofol em cada doente para detectar casos em que possa ocorrer uma diferença grande entre as concentrações calculadas de propofol e as concentrações reais medidas, de modo a identificar situações excepcionais que possam explicar possíveis insucessos na utilização do esquema, seja na sua concepção ou aplicação.

Período de colheita: 4-8 semanas + 4-8 semanas Número de casos: 40 + 30

- **Critérios de Selecção e Monitorização**

Os participantes deste estudo serão 40 +30 pacientes operados no bloco operatório de Neurocirurgia do HSA-CHP, com neurocirurgias programadas, ASA I-III, sujeitos a anestesia geral com intubação oro-traqueal realizada por laringoscopia e propostos para cirurgia da coluna. No dia anterior à cirurgia será obtido consentimento para o estudo e os doentes serão pesados numa balança de bioimpedância e medidos na enfermaria. A utilização da balança de bioimpedância visa obter os valores de massa gorda e massa muscular.

Por forma a assegurar a confidencialidade da identidade do paciente para cada um será criado um código o qual passará a ser usado em todos os dados recolhidos.

Este estudo não apresenta custos acrescidos para o CHP, uma vez que todos os dispositivos, monitores ou fármacos fazem parte da rotina habitual. Tal aplica-se também à administração de lidocaína e à eventual administração de efedrina para tratar a hipotensão arterial, o que é uma prática habitual.

O único procedimento não habitual é o doseamento de propofol no plasma. Para que se proceda à colheita será necessária uma agulha subcutânea de 25G, uma seringa de 5 mL e um tubo de colheita por cada doente. Quanto à determinação da concentração plasmática de propofol, nas amostras de sangue (uma por doente), esta amostra será enviada logo após a cirurgia à Faculdade de Farmácia onde será feita gratuitamente a análise nos laboratórios da faculdade por colaboração da Doutora Paula Guedes.

- **Critérios de Exclusão**

Excluem-se pacientes com IMC superior a 35 kg/m2, comorbilidades cardiovascular, hepática ou renal graves e idades inferiores a 18 ou superiores a 80 anos.

- **Procedimento**

PRIMEIRA FASE

Depois de deitados na mesa operatória, os doentes são cobertos por um lençol e por uma colcha dobrada a meio em cujo interior, e ao nível do abdómen, é colocado um dispositivo aquecedor com ar forçado, é cateterizada uma veia do dorso da mão esquerda e começa-se a infundir soro fisiológico a uma velocidade de 7ml/kg/h (se 60 kg dá 420 ml/h).

Serão então monitorizados os seguintes parâmetros: tensão arterial não invasiva (NIBP), oximetria de pulso (SpO2), frequência cardíaca (FC), electrocardiografia (ECG), índice biespectral (BIS), temperatura medida na ponta do dedo médio da mão esquerda e direita e bloqueio neuromuscular na mão direita. Se indicado pelo procedimento o uso de NIRS (oxigenação cerebral), colhe-se também os dados deste.

O registo contínuo destes parâmetros é feito através do programa Rugloop (Demed, Genk, Bélgica) instalado num computador dedicado. Este *software* comunica com o monitor Datex/GE para obter os dados da monitorização do doente e do BIS e com o sistema Fresenius Base Primea Orchestra que é utilizado para a administração de propofol. Com o *software* Rugloop obtém-se um ficheiro que regista, a cada 5 segundos, os valores das variáveis a estudar (TA, FC, SpO2, BIS, EMG, etc.) e as doses administradas e concentrações estimadas de propofol. Para a administração de propofol é selecionado o modelo farmacocinético de Schnider e o modo inicial "TCI View". Programa-se o módulo de propofol para iniciar a perfusão a 3,3ml/kg/h.

Procede-se a anestesia geral com bólus de Fentanil 3ug/kg seguido, quatro minutos depois, de bólus endovenoso de 20 mg de lidocaína com oclusão venosa por garrote colocado 20 cm acima do local da punção venosa, durante 40s (de forma a reduzir a dor provocada pela infusão de propofol e as respostas autonómicas à infusão do rocurónio [11,12] e administração de O_2 a 100% através de máscara facial. De seguida, inicia-se a infusão endovenosa de propofol a 1% a uma velocidade de 3,3 ml/kg/hora até à perda de consciência (LOC), momento identificado pela ausência de resposta do doente aos estímulos externos, nomeadamente quando deixa de abrir os olhos ou franzir o sobrolho em resposta ao chamamento e a um estímulo mecânico (bater na testa). O chamamento é efetuado a cada 10 segundos. Quando deixa de responder ao chamamento aplica-se o estímulo mecânico (acompanhado de chamamento) também a cada dez segundos.

Regista-se com rigor o momento de LOC. Após LOC o propofol passa a ser administrado por TCI com concentração cerebral (Ce) inferior à Ce no momento de LOC, de acordo com uma fórmula já publicada (75% da redução de manutenção) [8]. Esta redução decorre do facto de as concentrações necessárias para manter inconsciência serem inferiores às necessárias para induzir inconsciência.

De forma a determinar a concentração plasmática de propofol, dez minutos após LOC, é colhida uma amostra de sangue na artéria umeral esquerda, com cerca de 5 mL, com uma agulha subcutânea 25G. A amostra é colocada num tubo seco de tampa vermelha sem aditivos (*Cacuette* - referência 454092).

O monitor do bloqueio neuromuscular é calibrado e, de seguida é administrado rocurónio na dose de 0,6mg/kg. Quando já não se verificarem respostas ao TOF – Train-of-four (TOF igual a zero) realiza-se a laringoscopia e consequente intubação.

Após a intubação regula-se a concentração alvo de propofol de forma a manter o valor de BIS entre 40 e 60. Durante a cirurgia administra-se fentanil e rocurónio de acordo com as necessidades clínicas. A recolha de dados termina no momento da extubação traqueal.

SEGUNDA FASE

Nesta segunda fase serão estudados doentes utilizando os mesmos critérios de selecção e exclusão. A indução da anestesia será feita tal como na primeira fase até ao momento de LOC. Nesse momento será aplicado o esquema a desenvolver na primeira fase o qual resulta na determinação do ritmo de infusão de propofol em ml/h a efectuar depois de LOC. O BIS será monitorizado com alarmes entre 40 e 60. Se em qualquer momento o BIS exceder 60 o anestesista deverá intervir alterando a infusão de propofol. Se tal acontecer, o caso será considerado como um insucesso da utilização do novo esquema. Tal não prejudicará em nada o doente, uma vez que o nível adequado de anestesia será sempre assegurado pela intervenção do anestesista.

Pensamos que o novo esquema irá incluir uma regra que aplique duas ou três alterações da velocidade de administração de propofol nos trinta minutos iniciais.

Para a infusão de propofol será utilizada uma seringa Orchestra Base Primea em modo TCI view para poder recolher, através da Rugloop, os dados relativos á administração de propofol, nomeadamente as concentrações calculadas de propofol.

Será efectuada a colheita de uma amostra de sangue para doseamento de propofol plasmático igualmente dez minutos após LOC.

Trinta minutos após LOC o estudo termina e o anestesista decide como continuar a administração de propofol.

- **Tratamento dos dados**

Na primeira fase, os dados recolhidos para análise no sentido de obter o novo algoritmo são o momento de LOC, os valores de BIS e o volume de propofol infundido. Serão também analisados: tensão arterial, frequência cardíaca, SpO2, temperatura, oxigenação cerebral (se utilizada).

Todos estes dados serão tratados usando o *software* LABGRAB, exportados para Excel (1 ficheiro por paciente) e as médias e desvios padrão, calculados. De seguida, serão traçados modelos estatísticos que expressem relações (lineares, exponenciais ou logarítmicas) entre duas ou mais das variáveis recolhidas, com cálculo do R^2 como medida de ajustamento de cada modelo estatístico aplicado.

Da observação dos vários gráficos obtidos traçar-se-á um esquema que expresse a individualização da dose necessária após LOC para TIVA de fentanil por bólus e propofol em infusão; e a taxa de infusão para manutenção, de forma a obter-se um nível de anestesia adequado a cada paciente.

Na segunda fase será contabilizada a percentagem de tempo nos 30 minutos iniciais em que o BIS está entre 40 e 60 e o número de casos de insucesso na aplicação do novo esquema entendidos como necessidade de o anestesista alterar a administração de propofol.

Será relacionada a diferença entre a concentração calculada e a real de propofol e o grau de sucesso da aplicação do novo esquema.

Bibliografia

[1] Brüssel, T.; Theissen, J.; Vigfusson, G.; Lunkenheimer, P.; Aken, H.; and Lawin, P.; (1989) *Hemodynamic and Cardiodynamic Effects of Propofol and Etomidate: Negative Inotropic Properties of Propofol*. Anesthesia & Analgesia, 69:35-40

[2] Reich, D; Hossain, S.; Krol, M.; Baez, B; Patel, P.; Bernstein, A.; Bodia, C; (2005) *Predictors of Hypotension After Induction of General Anesthesia*. Anesthesia & Analgesia, 101:622

[3] Billard, V.; Moulla, F.; Bourgain, J; Megnigbeto, A.; Stanski, D; (1994) *Hemodynamic response to induction and intubation. Propofol/fentanyl interaction*. Anesthesiology, 81:1384-1393

[4] Leslie, K.; Clavisi, O.; (2008) *Target-controlled infusion versus manually-controlled infusion of propofol for general anaesthesia or sedation in adults*. Anesthesia & Analgesia, 107:2089

[5] Schraag, S.; Kreuer, S.; (2008) *Target-controlled infusion (TCI) - a concept with a future?: state-of-the-art, treatment recommendations and a look into the future*. Anaesthesia, 57 (3):223-30

[6] Miller, R.; Eriksson, L.; Fleisher, L.; Wiener-Kronish, J.; Young, W.; *Miller's Anesthesia,* 7ed., pp830-832. Philadelphia: Elsevier; 2010

[7] Roberts F.L., Dixons J., Lewis G.T.R., Tackley T.R., Prys-Roberts C. (1988) *Induction and Maintenance of Propofol Anaesthesia – A manual Infusion Scheme.* Anaesthesia, 3:14 – 17

[8] Castro, A.; Bressan, N.; Lobo, F.; Nunes, C.; Amorim P. (2008) *The higher the Propofol Concentration the Larger its Difference to the Concentrations Required at Maintenance, Using*

TCI and BIS Guided Anaesthesia. European Journal of Anaesthesiology, Volume 25, Supplement 44, p.150

[9] Tedim A., Pinto I., Amorim P., Castro A. (2013) *A New Scheme for Manual Infusion of Propofol, Allowing Individualization of Doses Required for Anesthesia Induction and Adequacy of the Initial Maintenance Rate*. SNACC

[10] Pinto, I.; Manso, T.; Carrapatoso, I.; Barros, A.; Amorim, P. (2013) *Influence of Patient Positioning on Hemodynamic and Cerebral Repercussions of Induction of General Anesthesia with Propofol*. SNACC

[11] Yew, S.; Chong, Y.; Tan H.; Goh, MH. (2005) *The effects of intravenous lidocaine on pain during injection of medium- and long-chain triglyceride propofol emulsions*. Anesthesia & Analgesia 100 (6):1693-5

[12] Memis, D.; Turan, A.; Karamanlıoglu, B.; Süt, N.; Pamukçu, Z. (2002) *The Prevention of Pain from Injection of Rocuronium by Ondansetron, Lidocaine, Tramadol, and Fentanyl*. Anesthesia & Analgesia 94:1517-1520

B_2 Informed Consent – New scheme for individualizing propofol induction and maintenance of general anesthesia



Estudos de investigação

Consentimento Informado



CONSENTIMENTO INFORMADO

NOVO ESQUEMA PARA INDIVIDUALIZAÇÃO DE PROPOFOL NA INDUÇÃO E MANUTENÇÃO DA ANESTESIA GERAL

Eu, abaixo-assinado _____, fui informado(a) de que o estudo de investigação acima mencionado consiste na administração de anestesia geral do modo que é utilizado habitualmente em operações de neurocirurgia neste hospital, consistindo o estudo no registo de dados para posteriormente desenvolver um esquema que proporcione a infusão de um nível de anestesia adequado a cada paciente. Os dados a registar são as doses do anestésico propofol administradas e os valores de um índice clínico chamado BIS, o qual é obtido através de um sensor colocado na testa e utilizado em todas as anestesias gerais como forma de avaliar, através do electroencefalograma, se a anestesia é adequada. Anestesia adequada consiste em manter o índice BIS entre 40 e 60 numa escala que vai de 0 a 100.

O estudo implica ainda a colheita de uma pequena amostra de sangue, realizada depois de estar anestesiado, para medir a concentração do anestésico propofol no sangue.

Todos os dados recolhidos serão anonimizados, e identificados com um código, preservando a confidencialidade e anonimato do doente, tendo-me sido garantido que todos os dados relativos à identificação dos participantes neste estudo são confidenciais.

Sei que posso recusar-me a participar ou interromper, a qualquer momento, a participação, sem nenhum tipo de penalização por este facto.

Compreendi a informação que me foi dada, tive oportunidade fazer perguntas e as minhas dúvidas foram esclarecidas.

Aceito participar de livre vontade no estudo acima mencionado ou autorizo de livre vontade a participação daquele que legalmente represento no estudo acima mencionado (conforme o caso).

Também autorizo a divulgação dos resultados obtidos no meio científico, garantindo o anonimato.

Nome do participante no estudo: _____

Assinatura _____ Data [/ /].

Nome do investigador responsável: _____

Assinatura _____ Data [/ /].



Estudos de investigação

Consentimento Informado



DOCUMENTAÇÃO DE INFORMAÇÃO AO DOENTE PARTICIPANTE NO ESTUDO

A operação de neurocirurgia a que vai ser submetido(a) implica anestesia geral. Para estas operações é usado um anestésico chamado propofol, o qual é administrado por via intravenosa, ao mesmo tempo que um soro, numa dose inicial para que o doente "fique a dormir" e depois de forma contínua ao longo de toda a operação para que se mantenha "a dormir".

Neste estudo vamos proceder à anestesia com propofol do modo como o fazemos habitualmente, mas iremos registar continuamente num computador a quantidade de propofol administrada e a evolução de alguns indicadores clínicos que também são obtidos sempre neste tipo de casos. Trata-se de tensão arterial, electrocardiograma e índice BIS.

Será também realizada uma recolha de sangue para se determinar a concentração de propofol no sangue, 10 minutos após o doente estar a dormir.

Com este estudo pretendemos obter dados que numa análise posterior permitam elaborar um esquema de infusão de propofol que possibilite a administração a cada paciente da quantidade adequada para o adormecer e manter anestesiado.

Contacto do Investigador Responsável

Ana Tedim (actedim@gmail.com)

+ 351 222 077 500

ext 1660



Estudos de investigação

Consentimento Informado



CONSENTIMENTO INFORMADO

NOVO ESQUEMA PARA INDIVIDUALIZAÇÃO DE PROPOFOL NA INDUÇÃO E MANUTENÇÃO DA ANESTESIA GERAL

Eu, abaixo-assinado _____, fui informado(a) de que o estudo de investigação acima mencionado consiste na administração de anestesia geral até adormecer, do modo que é utilizado habitualmente em operações de neurocirurgia neste hospital. Posteriormente a administração anestésica será dada segundo um novo esquema, sendo que se em qualquer momento o BIS exceder 60 ou for abaixo de 40, o anestesista poderá intervir e alterar a infusão do anestésico, da forma que lhe parecer a mais adequada. O valor de BIS é obtido através de um sensor colocado na testa e utilizado em todas as anestesias gerais como forma de avaliar, através do electroencefalograma, se a anestesia é adequada. Anestesia adequada consiste em manter o índice BIS entre 40 e 60 numa escala que vai de zero a cem. Os dados a registar serão o sucesso ou insucesso do esquema (caso o anestesista não tenha de intervir, então o esquema será registado como bem sucedido para este caso), a tensão arterial, o electrocardiograma, o índice BIS e quantidade de propofol administrada.

O estudo implica ainda a colheita de uma pequena amostra de sangue, realizada depois do paciente estar anestesiado, para medir a concentração do anestésico propofol no sangue.

Todos os dados recolhidos serão anonimizados, e identificados com um código preservando a confidencialidade e anonimato do doente, tendo-me sido garantido que todos os dados relativos à identificação dos participantes neste estudo são confidenciais.

Sei que posso recusar-me a participar ou interromper, a qualquer momento, a participação, sem nenhum tipo de penalização por este facto.

Compreendi a informação que me foi dada, tive oportunidade fazer perguntas e as minhas dúvidas foram esclarecidas.

Aceito participar de livre vontade no estudo acima mencionado ou autorizo de livre vontade a participação daquele que legalmente represento no estudo acima mencionado (conforme o caso).

Também autorizo a divulgação dos resultados obtidos no meio científico, garantindo o anonimato.

Nome do participante no estudo: _____

Assinatura _____ Data [/ /].

Nome do investigador responsável: _____

Assinatura _____ Data [/ /].



Estudos de investigação

Consentimento Informado



DOCUMENTAÇÃO DE INFORMAÇÃO AO DOENTE PARTICIPANTE NO ESTUDO

A operação de neurocirurgia a que vai ser submetido implica anestesia geral. Para estas operações é usada anestesia através do medicamento propofol, o qual é administrado por via intravenosa, ao mesmo tempo que um soro, numa dose inicial para que o doente "fique a dormir" e depois de forma contínua ao longo de toda a operação para que se mantenha "a dormir".

Neste estudo vamos proceder à anestesia com propofol do modo como o fazemos habitualmente até o paciente estar "a dormir", mas depois continuaremos a infusão do anestésico segundo um esquema que foi desenvolvido anteriormente com base em dados recolhidos de outros pacientes. A validação deste esquema será dada pelo facto dos valores de BIS se manterem dentro ou fora do intervalo considerado o adequado para o paciente (entre 40 e 60). Se em qualquer momento o BIS exceder 60 ou for abaixo de 40, o anestesista deverá intervir alterando a infusão de propofol. Se tal acontecer, o caso será considerado como um insucesso da utilização do novo esquema. Tal não prejudicará em nada o doente, uma vez que o nível adequado de anestesia será sempre assegurado pela intervenção do anestesista.

Iremos registar continuamente num computador a quantidade de propofol administrada e a evolução de alguns indicadores clínicos que também são obtidos sempre neste tipo de casos. Trata-se de tensão arterial, electrocardiograma e índice BIS. Será ainda anotado o sucesso ou insucesso do esquema.

Será também realizada uma recolha de sangue para se determinar a concentração de propofol no sangue, 10 minutos após o doente estar a dormir.

Com este estudo pretendemos validar o esquema desenvolvido de forma a podermos garantir que o paciente receberá a quantidade de anestésico adequada para o adormecer ou manter anestesiado.

Contacto do Investigador Responsável

Ana Tedim (actedim@gmail.com)

+ 351 222 077 500

ext 1660

B_3 Acceptance Letter – New scheme for individualizing propofol induction and maintenance of general anesthesia

NOVO ESQUEMA PARA INDIVIDUALIZAÇÃO DE PROPOFOL NA INDUÇÃO E MANUTENÇÃO DA ANESTESIA GERAL

064-14 (042-DEFI/ 063-CES) Projecto de Investigação

Data de Receção no Gabinete Coordenador da Investigação (GCI): 21/02/2014
Data de Envio do Parecer do GCI à Investigadora Principal: 27/02/2014
Data de Receção dos esclarecimentos: 17/04/2014
Reapreciação do Projecto e elaboração do Parecer Final: 17/04/2014

Investigadora Principal
Ana Rita Tedim – Investigadora, Agência para a competitividade e inovação (IAPMEI).

Investigador Responsável no Centro Hospitalar do Porto (CHP)
Pedro Amorim – Médico, Chefe de Serviço, Serviço de Anestesiologia do CHP.

Outros Investigadores
Ana Castro – Investigadora *PosDoc*, Instituto de Telecomunicações, Faculdade de Ciências da Universidade do Porto.

Resumo do Estudo:

- **Local do Estudo:** Serviço de Anestesiologia, Departamento de Anestesiologia, Cuidados Intensivos e Emergência do CHP.
- **Outras Instituições Intervenientes:** Instituto de Telecomunicações, Faculdade de Ciências da Universidade do Porto. Instituto de Ciências Biomédicas Abel Salazar da Universidade do Porto. Faculdade de Engenharia da Universidade do Porto. IAPMEI.
- **Desenho do estudo**: Institucional, clínico, aberto, prospetivo.
- **Objetivo 1ª fase**: Desenvolver um novo esquema, baseado num novo algoritmo, para a administração de propofol para indução e manutenção de anestesia sem recurso a modelos farmacocinéticos ou *target controlled infusion* (TCI).
- **Objetivo 2ª fase**: Validar o novo esquema através da sua aplicação na indução e manutenção anestésica.
- **Participantes no estudo:** Critérios de inclusão: Pacientes adultos, submetidos a procedimentos neurocirúrgicos (cirurgia da coluna), sob anestesia geral com intubação oro-traqueal e com estado físico I-III na classificação ASA; consentimento informado assinado. Critérios de exclusão: índice de massa corporal superior a 35 Kg/m^2; comorbilidades cardiovascular, hepática e renal graves; idade superior a 80 anos.
- **Tamanho da amostra**: Número esperado de doentes a recrutar no CHP na 1ª fase: 40 pacientes; na 2ª fase: 30 pacientes.
- **Duração do estudo**: Início em Março/2014; conclusão em Dezembro/2014.
- **Metodologia**: Os investigadores desenvolveram previamente um algoritmo para a indução anestésica que introduziu uma fórmula que indica qual a redução na concentração de propofol que deve ser aplicada para a manutenção adequada sem necessidade de TCI, em projeto de investigação realizado no CHP (referências 8-10 do documento de apresentação do projeto).
- De acordo com o objectivo da 1ª fase, durante o procedimento anestésico dos doentes recrutados será utilizado fentanil por bólus precedendo o propofol, seguido de propofol em infusão através de seringa perfusora elétrica sem sistema TCI. Será realizada a determinação da concentração

plasmática de propofol aos 10 minutos após *loss of consciousness* (LOC), para detectar casos em que possa ocorrer uma diferença grande entra as concentrações calculadas de propofol e as concentrações reais medidas. O procedimento anestésico restante será de acordo com a prática habitual. Os investigadores pretendem assim desenvolver um novo esquema anestésico que incorpore a capacidade de individualizar a dose de propofol adequada para cada indivíduo durante a indução e calcule a dose adequada para a manutenção da anestesia nos 30 minutos iniciais de modo a que o BIS esteja entre 40-60.

- Na 2ª fase, a indução anestésica será realizada como na 1ª fase até LOC. Nesse momento será aplicado o esquema desenvolvido na primeira fase, que permitirá determinar o ritmo de infusão de propofol em ml/h após LOC. O BIS será monitorizado como habitual, prevendo-se a intervenção do anestesista se exceder o valor de 60. Caso assim aconteça, será considerado como um insucesso da utilização do novo esquema. É garantida a protecção do doente dada a possibilidade de intervenção pelo anestesista. Haverá novamente colheita de sangue para determinação da concentração plasmática de propofol aos 10 minutos após LOC. Trinta minutos após LOC, o estudo termina e o anestesista determinará a forma de administração de propofol.
- Os pacientes participantes no estudo serão incluídos pelos anestesistas durante a visita pré-anestésica, após obtenção de consentimento informado.
- Na 1ª fase, os dados a recolher serão o momento de LOC, os valores de BIS, volume infundido de propofol, tensão arterial, frequência cardíaca, SpO2, temperatura e oxigenação cerebral. Na 2ª fase serão ainda registados a percentagem de tempo nos 30 minutos em que o BIS esteve entre 40 e 60 e o número de casos de insucesso na aplicação do novo esquema.
- É referido que o único procedimento não habitual no contexto do estudo será o doseamento plasmático do propofol. A amostra de sangue colhida (uma por doente) será enviada à Faculdade de Farmácia onde será efectuado gratuitamente o doseamento.
- São especificados os dados a recolher no estudo, clínicos e anestésicos, que serão registados de forma codificada. Está prevista a construção de uma base de dados anonimizada.
- Não haverá convocação de doentes especificamente no âmbito do estudo.
- São apresentados dois formulários de consentimento informado e dois documentos informativos do estudo para os participantes, separadamente de acordo com a fase do estudo.

Aspectos Financeiros

É referido que o projeto não apresenta custos específicos para o CHP.

Requisitos Preenchidos:

☑ Pedido de autorização dirigido ao Conselho de Administração, Comissão de Ética e DEFI.
☑ Termo de Responsabilidade e *Curriculum vitae* da Investigadora Principal (Dra. Ana Rita Tedim).
☑ Termo de Responsabilidade e *Curriculum vitae* do Investigador Responsável no CHP (Dr. Pedro Amorim).
☑ Autorização do Diretor de Serviço de Anestesiologia do CHP (Dr. Humberto Machado).
☑ Autorização do Diretor do Departamento de Anestesiologia, Cuidados Intensivos e Emergência do CHP (Dr. Fernando Rua)
☑ Documento de consentimento informado / Documento informativo sobre o estudo para os participantes no estudo
☑ Formulários para a recolha de dados

DEFI
DEPARTAMENTO DE ENSINO, FORMAÇÃO E INVESTIGAÇÃO

centro hospitalar do Porto

QUESTÕES CLARIFICADAS PELO INVESTIGADOR:

a) Os procedimentos a realizar no âmbito do estudo implicam riscos acrescidos para os doentes que aceitarem colaborar?

Conforme os esclarecimentos do Investigador (em anexo), "…não há riscos acrescidos para os participantes."

APRECIAÇÃO e PARECER FINAL do Gabinete Coordenador de Investigação/DEFI do CHP:

A proposta de investigação "*NOVO ESQUEMA PARA INDIVIDUALIZAÇÃO DE PROPOFOL NA INDUÇÃO E MANUTENÇÃO DA ANESTESIA GERAL"* foi reavaliada pelo Gabinete Coordenador de Investigação após esclarecimentos do investigador, tendo sido clarificada a questão colocada.

PARECER FAVORÁVEL pelo Gabinete Coordenador da Investigação.

Do ponto de vista científico, o Gabinete Coordenador de Investigação dá por concluída a análise do processo, sendo enviado ao Investigador o Parecer elaborado para conhecimento.

O processo segue para a Comissão de Ética para avaliação dos aspetos éticos, incluindo o Termo de Consentimento Informado e folheto informativo.

Deve ser aguardada a comunicação da autorização institucional para o início do estudo.

Centro Hospitalar do Porto, 17 de abril de 2014

_____

Isabel Fonseca,
Gabinete Coordenador de Investigação e em substituição da Diretora do DEFI

Appendix C

C_1 Clinical Protocol – Identification and characterization of neuromuscular reflections as indicators of detection of loss of consciousness in induction of general anesthesia with propofol in surgical patients

Protocolo Clínico

IDENTIFICAÇÃO E CARACTERIZAÇÃO DOS REFLEXOS NEUROMUSCULARES COMO INDICADORES DA DETECÇÃO DA PERDA DE CONSCIÊNCIA NA INDUÇÃO DE ANESTESIA GERAL COM PROPOFOL EM DOENTES CIRÚRGICOS

- **Introdução e Objectivos**

A anestesia geral é caracterizada pela indução de três efeitos: hipnótico (ausência de consciência), analgésica (ausência de dor) e paralisia (ausência de reflexos musculares). No caso específico da administração de fármacos hipnóticos, a indução da anestesia implica essencialmente produzir inconsciência, sendo o propofol o fármaco mais frequentemente usado para induzir esse estado. A perda de consciência (*Loss Of Consciensness* – LOC) é habitualmente avaliada por sinais clínicos e que advêm de escalas que resultam da observação do anestesiologista a respostas do doente a estímulos externos, como por exemplo abrir os olhos ao chamamento ou após um estímulo vigoroso (bater na testa).

Os efeitos secundários do propofol são já conhecidos, entre eles, repercussões hemodinâmicas, causando vasodilatação periférica e diminuição do débito cardíaco e, consequentemente, hipotensão arterial [1,2]. A tensão arterial verificada após a administração do propofol é normalmente 17% - 27% inferior ao seu valor basal [3]. Estes efeitos incidem com mais predominância em doentes de maior risco, como idosos, ou com menor reserva cardiovascular ou hipovolémicos. Os efeitos adversos obedecem, em geral, a uma ligação de proporcionalidade com as quantidades dos fármacos administradas por período de tempo. A quantidade de fármaco presente no doente é normalmente associada a uma concentração de fármaco a nível plasmático e de efeito, que no caso do propofol, é a concentração cerebral [3]. Por outro lado há muitas vezes necessidade de tratar a hipotensão com fármacos vasoativos e com fluidos para evitar a má perfusão dos órgãos vitais, nomeadamente quando já existe uma doença isquémica cardíaca, renal ou cerebral prévia que aumenta esse risco. Dadas estas condicionantes, existe a necessidade de administrar apenas a quantidade necessária de propofol para manter o doente inconsciente e minimizar efeitos secundários.

Na prática clínica comum, quando se administra propofol na forma de bólus, usam-se doses por kg de peso recomendadas e o propofol é por regra administrado numa injecção manual habitualmente realizada numa velocidade entre 900 e 1200 ml/h. Como consequência, é difícil identificar com precisão a quantidade de fármaco administrada nos momentos em que o doente deixa de responder a estímulos

externos ou quando os reflexos neuromusculares deixam de estar presentes. Uma forma de contornar este problema consiste em iniciar a anestesia com propofol com uma infusão lenta até que ocorra perda da consciência. Nesse momento suspende-se a administração, mas a concentração cerebral ainda continua a aumentar, devido ao fenómeno de histerese [6]. Durante a administração intravenosa e lenta de propofol, ocorre uma subida progressiva da concentração plasmática acompanhada, embora com um considerável atraso no tempo, de uma subida da concentração cerebral. O atraso na concentração cerebral de propofol em relação à plasmática é de cerca de 90 segundos. Desta forma, quando se interrompe de forma abrupta a infusão de propofol no momento de LOC, a concentração plasmática começa de imediato a diminuir, sendo que a cerebral continuará a subir, pois a concentração plasmática permanecerá durante algum tempo acima da cerebral até que ocorra um equilíbrio entre as duas concentrações. Assim, sempre que se cessa a administração do fármaco (no momento de LOC), a sua concentração no local de efeito continua a subir por algum tempo. Quanto maior a velocidade de administração, maior a diferença entre as concentrações plasmática e cerebral no momento em que se cessa a administração e maior o *overshooting* da concentração cerebral. O *overshooting* corresponde à diferença entre o pico de concentração cerebral e a concentração cerebral com que o paciente perdeu a consciência.

Com a utilização de uma velocidade de infusão lenta (gradual), é então possível monitorizar os momentos em que os diversos sinais clínicos que indicam um estado de consciência deixam de estar presentes. Durante a indução da anestesia, o doente vai perdendo gradualmente os reflexos neuromusculares de uma forma específica: 1º Deixa de manter os olhos abertos; 2º perde o reflexo palpebral; 3º não abre os olhos ao chamamento (deixa de obedecer conscientemente a comandos); 4º não abre os olhos a um estímulo externo vigoroso (bater na testa); 5º perde o reflexo corneano; 6º deixa de respirar de forma autónoma. Contudo, não só estes reflexos podem ser observados, como também o reflexo pupilar, que embora não seja normalmente utilizado para fins de perda de consciência, é um dos reflexos neuromotores de maior relevância clínica na prática médica para aceder ao nível de atividade cerebral do doente através da reatividade da pupila.

Na sua rotina, o clinico deteta estes reflexos de uma forma subjectiva, observando os diferentes movimentos das pálpebras ou da pupila do doente e a sua resposta ao chamamento, o que muitas vezes pode levar a erros de interpretação.

O objectivo deste estudo é utilizar monitorização adicional à normalmente disponível no bloco operatório do CHP, para poder estudar e analisar cada um destes reflexos de modo a objectivamente poder detectar o momento de perda de consciência (LOC). Com a finalidade de determinar o melhor monitor/reflexo ou combinação de reflexos que possa ser utilizado para medir objectivamente o momento de LOC em todos os doentes. Este estudo é apenas observacional de recolha de dados destes monitores,

dado não existir dados comparativos destas medições neste cenário.

Assim, tendo como base uma indução lenta de propofol, com o presente estudo pretendemos monitorizar os diversos reflexos neuromusculares utilizando monitores e equipamentos comerciais, já presentes no bloco operatório ou disponíveis no centro de investigação clinica em anestesiologia do CHP. Para cada um dos reflexos, será registado o momento em que este deixou de estar presente, assim como a quantidade de propofol infundida e as concentrações (plasmática e de efeito) correspondentes.

Para este estudo, serão recolhidos os dados durante 2 anos.

- **Critérios de Inclusão**

  - Os participantes deste estudo serão doentes consecutivos operados no bloco operatório de Neurocirurgia do HSA-CHP, com neurocirurgias programadas em que o médico anestesista seja um membro da equipa;
  - Doentes ASA I-III, sujeitos a anestesia geral por TIVA (total intravenous anaesthesia) utilizando como fármaco hipnótico o propofol
  - Possa ser aplicada a monitorização standard ASA recomendada para anestesias gerais

No dia anterior à cirurgia será obtido consentimento para o estudo e os doentes serão pesados numa balança de bioimpedância e medidos na enfermaria. A utilização da balança de bioimpedância visa obter os valores de massa gorda e massa muscular.

Por forma a assegurar a confidencialidade da identidade do paciente para cada um será criado um código o qual passará a ser usado em todos os dados recolhidos.

Este estudo não apresenta custos acrescidos para o CHP, uma vez que todos os dispositivos, monitores ou fármacos fazem parte da rotina habitual ou se encontram disponíveis ou cedidos ao centro de investigação.

- **Monitorização**

Os seguintes monitores da prática clinica deverão estar disponíveis para monitorização de rotina e validação dos reflexos:

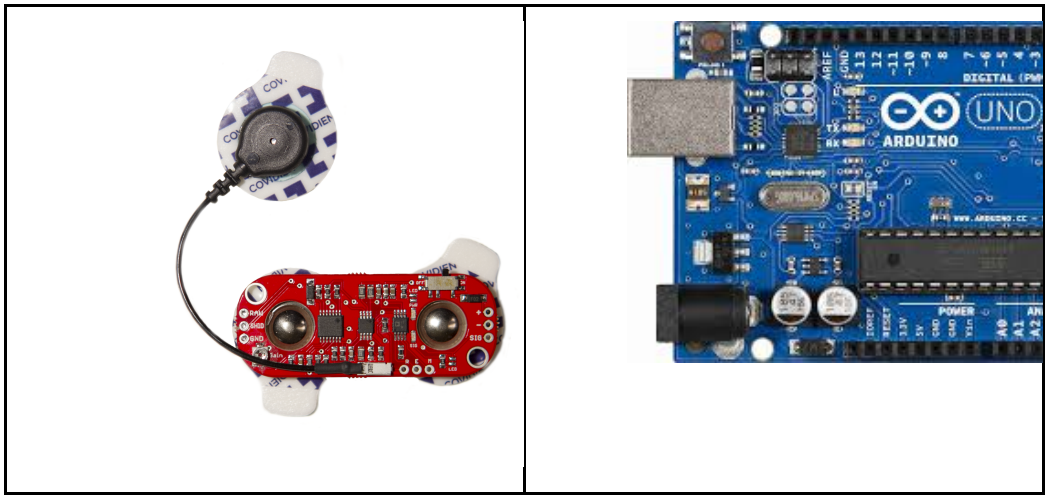
- Monitor de anestesia (incluindo ventilador) Aisys da GE
- Monitor de BIS VISTA Bilateral (monitor de EEG)
- Monitor ANI (Analgesia Nociception Index, que fornece um índice de nocicepção sobre a Variabilidade R-R)

- Monitorização do nível de bloqueio neuromuscular de preferência com o Monitor TOF Watch SX.
- Monitorização da oxigenação cerebral com o monitor INVOS
- Seringas perfusoras Fresenius Base Primea Orchestra, para os fármacos anestésicos

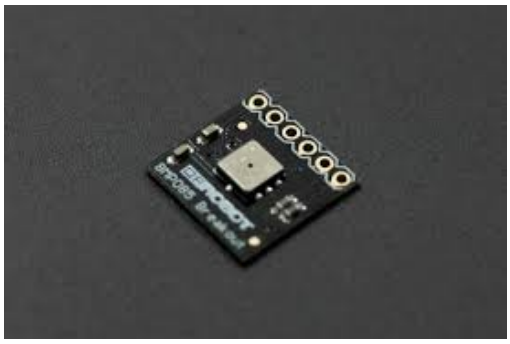
De seguida explica-se a minitorização adicional especifica deste estudo.

Para a monitorização da eletromiografia (EMG) do músculo orbicular será usado um sistema MioWare (Figura 1), ligado a um microcontrolador Arduino Uno (Figura 2). A EMG permite verificar a a presença ou ausência da contração da pálpebra e inferir se existe a presença do reflexo neuromuscular.

A atividade do músculo orbital, responsável pelo fecho da palpebral, pode ser monitorizada através da aplicação de sensores de eletromiografia que indicaram o grau de atividade muscular. Assim, se o doente responder a algum dos estímulos anteriores, teremos acesso a uma medida objetiva sobre se houve realmente uma resposta.



A ausência de resposta do doente a comandos verbais é monitorizada através de uma ação simples, como segurar um objeto pesado ou realizar uma tarefa, como apertar uma seringa de 50cc. Para a monitorização da ação comportamental de apertar uma seringa com a mão durante a fase de indução, será utilizado um sensor de pressão Barometric Pressure Sensor BMP085, da DFRobot. (Figura 3), também ligado ao mesmo microcontrolador Arduino Uno.



Para realizar a estimulação do nervo supraorbital será utilizado um sistema TOF-Watch SX,da empresa Organon, monitor de relaxamento muscular utililizado regularmente no CHP. (Figura 4).



Para a monitorização do reflexo pupilar será utilizado um pupilómetro AlgiScan (Figura 5) para quantificação do reflexo pupilar à luz e do reflexo pupilar à estimulação eléctrica. Este pupilómetro comercial permite verificar a dilatação e a contração da pupila, através da variação do seu diâmetro.



Será também utilizado um microfone de contacto TSD108, da BioPac (Figura 6), para medir a frequência respiratória e também determinar quando é que o doente deixa de respirar de forma autónoma (6º Reflexo), como consequência da anestesia.

- **Critérios de Exclusão**

Excluem-se pacientes com IMC superior a 35 kg/m2, comorbilidades cardiovascular, hepática ou renal graves e idades inferiores a 18 ou superiores a 80 anos.

- **Procedimento**

Os doentes seguem a rotina habitual de entrada e instalação do bloco operatório. E são monitorizados conforme o protocolo clinico de rotina, com a colocação de eléctrodos acessos de fármacos.

Segue-se a explicação da monitorização adicional deste estudo:

- São colocados dois eletrodos para estimulação do nervo supraorbital e mais três para leitura do potencial muscular, conforme ilustrado na Figura 7.

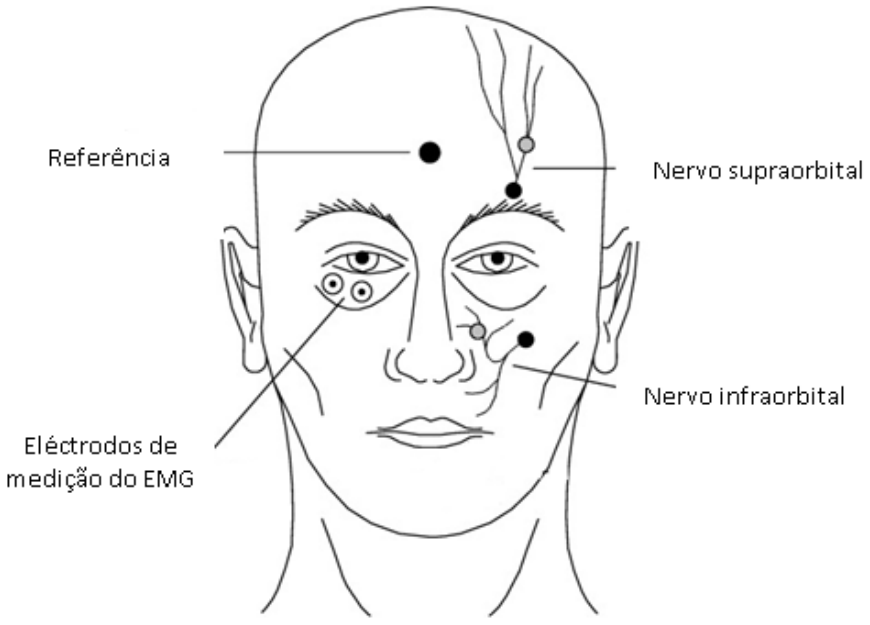


Figura 7: Configuração para colocar os sensores dos reflexos neuromusculares.

Antes do ínicio da indução, e no que diz respeito à estimulação para determinar o LOC, liga-se o sistema TOF-Watch SX para estimular o nervo supraorbital. Colocam-se também os electródos que servirão para monitorizar o potencial muscular (Eletromiografia – EMG) gerado pela resposta à estimulação do nervo supraorbital. O sinal de EMG é adquirido utilizando um sistema composto por um sistema MioWare ligado a um microcontrolador Arduino UNO e conectado a uma aplicação desenvolvida em LabVIEW 2014.

- Pede-se ao doente que inicie o processo de apertar a seringa de 50 cc sempre que fizer uma inspiração.

O protocolo clinico de indução da anestesia, é o da prática habitual com uma infusão gradual de propofol (ou seja sem bolus ou por TCI). As doses a serem utilizadas de propofol, do analgésico intravenoso ou do relaxante muscular serão as adequadas ao doente e tritadas pelo médico anestesista.

- Assim que é atingida uma quantidade infundida mínima de 0.5 mg/kg de propofol, inicia-se a estimulação do nervo supraorbital a cada 10 segundos, sendo o objetivo principal detetar o momento em que se perde o reflexo corneano. Para tal, entre cada estímulo, pode ser verificada a presença do reflexo através da gota de soro na córnea, para fins de validação experimental.

Deve-se mnater a mesma velocidade de infusão de propofol até LOC, momento identificado pela ausência de resposta do doente a um estímulo externo vigoroso (bater na testa). A verificação da resposta é efetuada a cada 10 segundos. Quando o doente deixa de responder ao chamamento aplica-se o estímulo mecânico (acompanhado de chamamento) também a cada 10 segundos.

Regista-se com rigor o momento em que cada reflexo deixou de estar presente.

Após LOC o propofol passa a ser administrado por TCI com concentração cerebral (Ce), durante a manutenção o propofol deverá ser tritado seguindo os procedimento standard para manter um nível de BIS recomendado entre [40-60], segundo as recomendações ASA.

Durante a cirurgia administra-se o analgésico e o relaxante muscular de acordo com as necessidades clínicas. A recolha de dados termina no momento da extubação traqueal.

Serão monitorizados os seguintes parâmetros: tensão arterial não invasiva (NIBP), oximetria de pulso (SpO2), frequência cardíaca (FC), electrocardiografia (ECG), índice biespectral (BIS), temperatura medida na ponta do dedo médio da mão esquerda e direita e bloqueio neuromuscular na mão direita. Será também monitorizado o nível de oxigenação cerebral, com recurso ao monitor INVOS, e o nível de nocicepção com recurso ao monitor ANI. Os dados referentes às infusões de propofol e remifentanil (analgésico mais

habitual), rocurónio (relaxante muscular mais habitual), como volumes infundidos, taxas de infusão e concentrações plasmáticas e de efeito estimadas, serão também armazenados.

O registo contínuo dos parâmetros hemodinâmicos é feito através do programa Rugloop (Demed, Genk, Bélgica) instalado num computador dedicado. Este *software* comunica com o monitor Aisys/GE para obter os dados da monitorização do doente e do BIS e com o sistema Fresenius Base Primea Orchestra que é utilizado para a administração de propofol. Os dados do monitor TOF Watch SX e do AlgisScan também permitem a importação para o computador.

- **Tratamento dos dados**

Os dados obtidos pelas respostas dos reflexos neuromusculares serão analisados offline para avaliar se algum dos parâmetros registados exibe alterações que se correlacionem com a perda de consciência.

Os dados serão também analisados para identificar qual dos parâmetros de monitorização registados melhor se correlaciona com o momento de LOC, detetado pelo método clínico de bater na testa do doente.

Será também avaliada a relação entre o valor das diferentes variáveis monitorizadas no momento de LOC, bem como a quantidade de propofol necessária para produzir inconsciência.

Os dados recolhidos para análise são o momento de LOC, os valores de BIS e o volume de propofol infundido. Serão também analisados: tensão arterial, frequência cardíaca, SpO2, temperatura, oxigenação cerebral (se utilizada).

Todos estes dados serão tratados usando o software LABGRAB, exportados para Excel (um ficheiro por paciente) e as médias e desvios padrão, calculados. De seguida, serão traçados modelos estatísticos que expressam relações (lineares, exponenciais ou logarítmicas) entre duas ou mais das variáveis recolhidas, com cálculo do R2 como medida de ajustamento de cada modelo estatístico aplicado.

A segunda fase a análise dos dados tem por objectivos:

1. Avaliar o grau de sucesso dos reflexos neuromusculares na determinação de LOC, sendo que um sucesso corresponde a avaliação clínica confirmar a perda de consciência;
2. Comparar, no período entre paragem de administração de propofol e intubação traqueal, os valores de BIS e TS entre os casos dos doentes de “aparente sucesso” e os casos da dos doentes da primeira fase do estudo, de modo a detetar um possível atraso na deteção de LOC quando esta é identificada através dos reflexos neuromusculares;
3. Comparar os valores de TA no momento de LOC e de TA mínima durante o estudo de modo a ver se a utilização dos reflexos neuromusculares resultaria em menos hipotensão;
4. Comparar a variação de TA, FC, BIS, EMG, TS e pletismografia nas duas fases do estudo de

modo a avaliar se a utilização dos reflexos neuromusculares e eventualmente de menor quantidade de propofol assegura um nível adequado de anestesia durante a intubação traqueal, avaliando se ocorrem subidas de TA ou FC superiores a 20% em relação ao basal ou subida do BIS acima de 60 ou descida da pletismografia superior a dois pontos.

5. Contabilizada a percentagem de tempo nos 30 minutos iniciais em que o BIS está entre 40 e 60 e o número de casos de insucesso na aplicação do novo esquema entendidos como necessidade de o anestesista alterar a administração de propofol.

Quaisquer efeitos adversos serão registados e reportados.

Será efetuada análise estatística na comparação dos resultados.

Prevê-se a apresentação de resultados através de comunicações científicas em dois congressos nacionais e dois internacionais, nas áreas da engenharia e da anestesiologia. Prevê-se a publicação de dois artigos científicos em revistas internacionais, um mais técnico na área da engenharia e um com os resultados clínicos numa revista de anestesiologia.

Bibliografia

[1] Brüssel, T.; Theissen, J.; Vigfusson, G.; Lunkenheimer, P.; Aken, H.; and Lawin, P.; (1989) *Hemodynamic and Cardiodynamic Effects of Propofol and Etomidate: Negative Inotropic Properties of Propofol*. Anesthesia & Analgesia, 69:35-40

[2] Reich, D; Hossain, S.; Krol, M.; Baez, B; Patel, P.; Bernstein, A.; Bodia, C; (2005) *Predictors of Hypotension After Induction of General Anesthesia*. Anesthesia & Analgesia, 101:622

[3] Billard, V.; Moulla, F.; Bourgain, J; Megnigbeto, A.; Stanski, D; (1994) *Hemodynamic response to induction and intubation. Propofol/fentanyl interaction*. Anesthesiology, 81:1384-1393

[4] Leslie, K.; Clavisi, O.; (2008) *Target-controlled infusion versus manually-controlled infusion of propofol for general anaesthesia or sedation in adults*. Anesthesia & Analgesia, 107:2089

[5] Schraag, S.; Kreuer, S.; (2008) *Target-controlled infusion (TCI) - a concept with a future?: state-of-the-art, treatment recommendations and a look into the future*. Anaesthesia, 57 (3):223-30

[6] Miller, R.; Eriksson, L.; Fleisher, L.; Wiener-Kronish, J.; Young, W.; *Miller's Anesthesia,* 7ed., pp830-832. Philadelphia: Elsevier; 2010

[7] Roberts F.L., Dixons J., Lewis G.T.R., Tackley T.R., Prys-Roberts C. (1988) *Induction and Maintenance of Propofol Anaesthesia – A manual Infusion Scheme.* Anaesthesia, 3:14 – 17

[8] Castro, A.; Bressan, N.; Lobo, F.; Nunes, C.; Amorim P. (2008) *The higher the Propofol Concentration the Larger its Difference to the Concentrations Required at Maintenance, Using TCI and BIS*

Guided Anaesthesia. European Journal of Anaesthesiology, Volume 25, Supplement 44, p.150

[9] Tedim A., Pinto I., Amorim P., Castro A. (2013) *A New Scheme for Manual Infusion of Propofol, Allowing Individualization of Doses Required for Anesthesia Induction and Adequacy of the Initial Maintenance Rate*. SNACC

[10] Pinto, I.; Manso, T.; Carrapatoso, I.; Barros, A.; Amorim, P. (2013) *Influence of Patient Positioning on Hemodynamic and Cerebral Repercussions of Induction of General Anesthesia with Propofol*. SNACC

[11] Yew, S.; Chong, Y.; Tan H.; Goh, MH. (2005) *The effects of intravenous lidocaine on pain during injection of medium- and long-chain triglyceride propofol emulsions*. Anesthesia & Analgesia 100 (6):1693-5

[12] Memis, D.; Turan, A.; Karamanlıoglu, B.; Süt, N.; Pamukçu, Z. (2002) *The Prevention of Pain from Injection of Rocuronium by Ondansetron, Lidocaine, Tramadol, and Fentanyl*. Anesthesia & Analgesia 94:1517-1520

C_2 Informed Consent – Identification and characterization of neuromuscular reflections as indicators of detection of loss of consciousness in induction of general anesthesia with propofol in surgical patients



CONSENTIMENTO INFORMADO INFORMAÇÃO AO DOENTE

IDENTIFICAÇÃO E CARACTERIZAÇÃO DOS REFLEXOS NEUROMUSCULARES COMO INDICADORES DA DETECÇÃO DA PERDA DE CONSCIÊNCIA NA INDUÇÃO DE ANESTESIA GERAL COM PROPOFOL EM DOENTES CIRÚRGICOS

Eu, _____(NOME COMPLETO DO INDIVÍDUO PARTICIPANTE DO ESTUDO):

Fui informado de que o Estudo de Investigação acima mencionado se destina a monitorizar diversos reflexos como a perda de reflexo visual, palpebral, movimento. De modo a determinar melhor o momento de perda de consciência durante a indução da anestesia e antes da cirurgia começar.
Sei que neste estudo está prevista a utilização de monitores e sensores que não são habituais, tendo-me sido explicado em que consistem.
Foi-me garantido que todos os dados relativos à identificação dos Participantes neste estudo são confidenciais e que será mantido o anonimato.
Sei que posso recusar-me a participar ou interromper a qualquer momento a participação no estudo, sem nenhum tipo de penalização por este facto.
Compreendi a informação que me foi dada, tive oportunidade de fazer perguntas e as minhas dúvidas foram esclarecidas.
Aceito participar de livre vontade no estudo acima mencionado
Também autorizo a divulgação dos resultados obtidos no meio científico, garantindo o anonimato.

Nome do Participante no estudo

Data Assinatura

___/___/_____ _____

Nome do Médico Responsável ou Nome do Investigador Responsável

Data Assinatura

___/___/_____ _____

INFORMAÇÃO AO DOENTE

Estudo Clínico: IDENTIFICAÇÃO E CARACTERIZAÇÃO DOS REFLEXOS NEUROMUSCULARES COMO INDICADORES DA DETECÇÃO DA PERDA DE CONSCIÊNCIA NA INDUÇÃO DE ANESTESIA GERAL COM PROPOFOL EM DOENTES CIRÚRGICOS

A indução da anestesia implica essencialmente produzir inconsciência, sendo o propofol o fármaco mais frequentemente usado para induzir esse estado. A perda de consciência é habitualmente avaliada por sinais clínicos e que advêm de escalas que resultam da observação do anestesiologista a respostas do doente a estímulos externos, como por exemplo observando os diferentes movimentos das pálpebras ou da pupila do doente, abrir os olhos ao chamamento ou após um estímulo vigoroso (bater na testa).

O objectivo deste estudo é utilizar monitorização adicional à normalmente disponível no bloco operatório do CHP, para poder estudar e analisar alguns reflexos do doente de modo a objectivamente poder detectar o momento de perda de consciência. Com a finalidade de determinar o melhor monitor/reflexo ou combinação de reflexos que possa ser utilizado para medir objectivamente o momento de perda de consicência em todos os doentes.

Este estudo é apenas observacional de recolha de dados destes monitores e não interfere com a prática clinica habitual ou com o o procedimento anestésico ou cirúrgico.

Todos os dados relativos à identificação dos Participantes neste estudo são confidenciais e que será mantido o anonimato.

O doente pode recusar-se a participar ou interromper a qualquer momento a participação no estudo, sem nenhum tipo de penalização por este facto.

A divulgação dos resultados obtidos será feita apenas no meio científico, garantindo o anonimato.

C_3 Acceptance Letter – Identification and characterization of neuromuscular reflections as indicators of detection of loss of consciousness in induction of general anesthesia with propofol in surgical patients

IDENTIFICAÇÃO E CARACTERIZAÇÃO DOS REFLEXOS NEUROMUSCULARES COMO INDICADORES DA DETEÇÃO DA PERDA DE CONSCIÊNCIA NA INDUÇÃO DE ANESTESIA GERAL COM PROPOFOL EM DOENTES CIRÚRGICOS

068-17 (062-DEFI/062-CES) Projeto de investigação

Data de Receção no Gabinete Coordenador da Investigação (GCI): 11/04/2017

Investigador Principal e Responsável no Centro Hospitalar do Porto (CHP):

- Pedro Amorim – Médico Anestesista, Serviço de Anestesiologia, Departamento de Anestesiologia, Cuidados Intensivos e Emergência (DACIE) do CHP.

Outros investigadores:

- Catarina Nunes – Professora Auxiliar na Universidade Aberta e Investigadora Principal do Centro de Investigação Clínica em Anestesiologia do CHP;
- Ana Leitão Ferreira – Faculdade de Engenharia, Aluna de Doutoramento e Investigadora do Centro de Investigação Clínica em Anestesiologia do CHP.

Resumo do Estudo:

- **Local do Estudo no CHP:** Serviço de Anestesiologia, DACIE do CHP.
- **Desenho do estudo**: Clínico, nacional, institucional, descritivo, observacional, transversal e prospetivo.
- **Objetivos**: 1) Utilizar monitorização adicional à normalmente disponível no bloco operatório do CHP para estudar e analisar diversos reflexos neuromusculares de modo a detetar objectivamente o momento de perda de consciência (LOC – *Loss of Consciensness*), determinando o melhor monitor/ reflexo ou combinação de reflexos que a ser utilizado; 2) Avaliar, durante a manutenção da anestesia geral, a presença de atividade electromiográfica dos músculos frontais e o seu impacto na índice BIS.
- **Participantes no estudo**: *Critérios de inclusão* - Doentes consecutivos operados no bloco operatório de Neurocirurgia do HSA-CHP, com neurocirurgias programadas em que o médico anestesista seja um membro da equipa; doentes ASA I-III, sujeitos a anestesia geral por TIVA (total intravenous anaesthesia) utilizando como fármaco hipnótico o propofol, doentes em que possa ser aplicada a monitorização standard ASA recomendada para anestesias gerais. *Critérios de exclusão* - Pacientes com IMC superior a 35 kg/m^2, comorbilidades cardiovascular, hepática ou renal graves e idades inferiores a 18 ou superiores a 80 anos.
- **Tamanho da amostra**: não estimado.
- **Duração do estudo**: Início 01/05/2017; conclusão 01/05/2019.
- **Metodologia**:
  - Os Investigadores pretendem fazer recolha de dados clínicos dos doentes participantes, através de monitorização adicional à normalmente utilizada no bloco operatório, de diversos reflexos neuromusculares, durante a realização do procedimento anestésico ou cirúrgico.
  - O recrutamento dos participantes e a recolha dos dados clínicos depreende-se que serão realizados sob supervisão do Dr. Pedro Amorim, no âmbito da prática clínica habitual, não interferindo com o procedimento cirúrgico ou anestésico.
  - Foi enviado o termo de consentimento informado, bem como o documento informativo sobre o estudo para o participante.
  - No dia anterior à cirurgia será obtido consentimento para o estudo e os doentes serão pesados numa balança de impedância (para obter valores de massa gorda e massa muscular) e medidos na enfermaria.





- Durante o procedimento cirúrgico, os diversos reflexos neuromusculares serão monitorizados utilizando monitores e equipamentos comerciais, já presentes no bloco operatório e disponíveis no centro de investigação clínica em anestesiologia do CHP.
- No bloco operatório, os doentes serão monitorizados conforme o protocolo clínico de rotina e para a monitorização adicional do estudo, serão colocados 2 eléctrodos para a estimulação do nervo supraorbital e mais 3 para leitura do potencial muscular.
- A ausência de resposta do doente a estímulos externos vigorosos (bater na testa) ou a comandos verbais (aperto de uma seringa na mão) serão também monitorizados.
- Para cada um dos reflexos será registado o momento em que este deixou de estar presente, assim como a quantidade de propofol infundida (infusão gradual) e as concentrações (plasmática e de efeito) correspondentes.
- Para relaxamento muscular será usado o medicamento Rocurónio na dose inicial para intubação traqueal (0,6 mg/kg). A recolha de dados termina com a extubação traqueal.
- Não foi enviado um formulário de registo de dados, mas foram indicadas as variáveis a colher para análise: momento de LOC, valores de BIS e volume de propofol infundido, tensão arterial frequência cardíaca (FC), oximetria de pulso (SpO2), temperatura, oxigenação cerebral.
- Os dados colhidos serão tratados usando o *software* LABGRAB e modelos estatísticos, para posterior análise comparativa.
- Foi referida a criação de uma base de dados anonimizada.
- São garantidas a proteção da identidade dos participantes e a confidencialidade dos dados recolhidos (criação de um código usado em todos os dados recolhidos).

Aspectos financeiros:

O estudo não apresenta custos acrescidos para o CHP, uma vez que todos os dispositivos, monitores ou fármacos fazem parte da rotina habitual ou se encontram disponíveis ou cedidos ao centro de investigação clínica em anestesiologia do CHP.

Requisitos Preenchidos:

☑ Pedidos de autorização dirigidos ao Conselho de Administração, Comissão de Ética para a Saúde e Departamento de Ensino, Formação e Investigação.
☑ Termo de Responsabilidade do Investigador Principal/ Responsável no CHP (Dr. Pedro Amorim).
☑ Autorização do Diretor do Serviço de Anestesiologia (Prof. Doutor Humberto Machado).
☑ Autorização do Diretor do DACIE do CHP (Dr. António Marques).
☑ Consentimento informado para o doente.
☑ Informação para o doente.

APRECIAÇÃO e PARECER FINAL do GABINETE COORDENADOR DE INVESTIGAÇÃO do CHP:

A proposta de investigação "Identificação e caracterização dos reflexos neuromusculares como indicadores da deteção da perda de consciência na indução de anestesia geral com propofol em doentes cirúrgicos" foi avaliada pelo Gabinete Coordenador de Investigação, não havendo dúvidas ou questões a esclarecer.

PARECER FAVORÁVEL pelo Gabinete Coordenador da Investigação.





O Gabinete Coordenador de Investigação dá por concluída a análise do processo, sendo enviado ao Investigador Principal o Parecer elaborado para conhecimento.

O processo segue para a Comissão de Ética para avaliação dos aspetos éticos, nomeadamente o termo de consentimento informado e o documento informativo sobre o estudo.

Deve ser aguardada a comunicação da autorização institucional para a realização do estudo.

Centro Hospitalar do Porto, 18 de abril de 2017

_____

Márcia Oliveira, Gabinete Coordenador de Investigação

_____

Isabel Fonseca, Responsável pela área dos Estudos de Investigação,
DEFI/ Gabinete Coordenador de Investigação