The Effect of Ketamine on Depth of Hypnosis Indices During Total Intravenous Anesthesia – a Comparative Study Using a Novel Case Replay System

Bachelor's Thesis
Biomedical Engineering

by

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ABSTRACT

Introduction: Processed electroencephalogram (pEEG) monitors provide clinical information by deriving a depth-of-hypnosis (DoH) index from the complex EEG signal. Ketamine, frequently used during surgery to reduce postoperative pain, is known to affect high frequency EEG power, particularly in the high beta and low gamma (24-32 Hz) range. Thus, DoH indices may become unreliable when ketamine is used. The purpose of this study was to compare the effects of ketamine on three commonly used DoH monitors by extending our EEG simulator to allow faithful replay of previously recorded EEG.

Methods: Research Ethics Board approval was obtained for secondary use of EEG data from a randomized controlled trial of total intravenous anesthesia with ketamine, with three groups: Group 0.5 [receiving ketamine, 0.5 $mg \cdot kg^{-1}$ bolus, 10 $mcg \cdot kg^{-1} \cdot min^{-1}$ infusion], Group 0.25 [receiving ketamine, 0.25 $mg \cdot kg^{-1}$ bolus, 5 $mcg \cdot kg^{-1} \cdot min^{-1}$ infusion], and Control Group [no ketamine]. EEG data were replayed to three monitors: NeuroSENSE (NeuroWave Systems, DoH index = WAV), BIS (Medtronic, DoH index = BIS) and Entropy (GE Healthcare, DoH index = SE). Differences in DoH indices in the initial 15 min of case, during which peak ketamine DoH effect was expected to be observed, were presented as violin plots, in 30 second intervals, for the three devices. Furthermore, DoH differences between the each of the two ketamine groups and the control group were compared, in 5 minute intervals, using the Wilcoxon rank-sum test; similarly, differences between the monitors for each dosage group were explored. Finally, Bland-Altman analysis was used for pairwise comparison of agreement between the three DoH monitors.

Results: Data were available for 27 cases. The presence of ketamine significantly increased the DoH index after induction of anesthesia for all three monitors. Compared to the control group, the median difference (MD) after induction, calculated over a one minute window, for Group 0.5 were 13.9, 16.0, and 15.5, for BIS, SE, and WAV respectively; similarly, MD for Group 0.25 were 13.3, 16.0, and 14.8, for BIS, SE, and WAV respectively (all $p<0.025$). Comparing the MDs between monitors within each dosage group, no significant differences were found in either ketamine group. The presence of ketamine did not alter the agreement between any pair of monitors.

Conclusion: Regardless of the monitor used, the evaluated bolus doses of ketamine rendered the DoH indices temporarily unreliable. The observed DoH increase was likely caused by a power increase in the beta and gamma bands. However, there were no lasting significant differences between DoH in the three monitors, which is clinically reassuring.

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INTRODUCTION

CHAPTER 1

The following section is intended to briefly introduce the necessary background information on general anesthesia, depth of hypnosis monitors, and ketamine to contextualize our research in the domain of current technical and medical practice.

1.1 Adequacy of General Anesthesia

General anesthesia (GA) is a reversible, drug-induced comatose state which is characterized by the interplay of the four components of anesthesia: hypnosis, amnesia, analgesia, and akinesia.[1] During GA the patient is unconscious (hypnosis), unable to form memories (amnesia), insensitive to pain (analgesia), and not capable of muscle movement (akinesia). The depth of anesthesia is considered adequate when the concentrations of drugs are sufficient to provide comfort for the patient and perform medical procedures.[2] Ideally, monitoring would reflect each end point of anaesthesia quantitatively. Currently, except for akinesia measured with train-of-four monitors, no other end point of anesthesia can be directly assessed. Furthermore, the exact mechanism of anesthesia still remains unclear. So far, the measured parameters can only indirectly assess the end points of anesthesia and provide partial insights to a much more complex system.[3]

Traditional monitoring of anesthesia takes into account various physical reactions (e.g. circulation, respiration, eye-reaction, and movement) to assess anesthetic depth and control medication to avoid the consequences of under- (e.g. intraoperative awareness) or over-dosing (e.g. delayed emergence) the patient.[4] Many attempts have been made to objectively and quantitatively measure the adequacy of anesthesia. Clinically observed reactions of the autonomic nervous system related to stress, such as an increase in blood pressure, heart rate, sweating, and tearing are considered when assessing the adequacy of anesthesia. The PRST score (pressure, rate, sweating, tears), proposed by Evans, offers a standardization to assess autonomic reaction.[5] Changes with respect to the baseline at the awake state are scored between 0 and 2 for all four categories. A PSRT score, which is the sum of all four individual scores (range: 0-8), greater than 2 is considered an indicator for too light anesthesia. However, the PRST scoring system has demonstrated a huge variability and low agreement with the clinical assessment of anesthesia adequacy.[6]

Another attempt to assess the depth of anesthesia both objectively and quantitatively includes the recording and analysis of electrical brain activity, as a complement to traditional clinical monitoring. Its primary goal is to personalize anesthesia to individual needs so patients can recover more rapidly and are exposed to a lower risk of awareness.

1.2 Brain Activity During General Anesthesia

In 1929, the German psychiatrist Hans Berger published the first systematic report of electrical signals recorded from the human scalp; thus, the electroencephalography (EEG) was born.[7] Only a few years later, Gibbs *et al*. identified characteristic patterns caused by anesthetic agents on the human electroencephalogram.[8] Since then, the progressive nature of EEG changes during stages of anesthesia have been widely studied; nevertheless, the precise mechanism remain unclear.

Increased amplitude, slower EEG frequencies, as well as overall reduced neuronal firing, and increased synchrony are generally associated with deepening of anesthesia.[4] At deeper stages, alternation between bursts and periods of isoelectric signal occur; an EEG pattern known as burst suppression. It is quantified by using the burst suppression ratio (BSR) which is a measure of the fraction of time spent in suppression per period.[9] Higher dosages of hypnotic agents are linked to isoelectricity (i.e. flat EEG).

Nevertheless, monitoring EEG in its raw form is not common practice in the operation room. There are several reasons for this: Firstly, the raw signal is too complex for the untrained eye to read. Secondly, even for a highly trained clinician information is often hindered by interpersonal variations, and low signal to noise ratio (SNR).[10] Artifacts affecting the signal can be of physiological (e.g. muscle activity, eye movements, respiratory artifacts, and skin conductance artifact caused by sweating) or extra-physiological (e.g. detached electrodes, 50/60-Hz artifacts, or artifacts induced by electrosurgery) origin.[11] The high complexity of the signal, its sensitivity to perturbations, and interpretation difficulties create the need for simplification. Processed EEG (pEEG) simplifies complex waveforms into clinically usable measures of depth of anesthesia – by focusing on certain aspects of the signal such as frequency, phase, and amplitude. Traditional monitoring during anesthesia takes into account various physical reactions (e.g., circulation, respiration, eye-reaction, and movement) to assess anesthetic depth and control medication. The expectation is that EEG-based

monitoring of anesthetic depth, as a complement to traditional monitoring, will improve the potential to adapt anesthesia to individual patient needs during the course of surgery.

1.3 Basic Principles of Depth of Hypnosis Monitors

Depth of hypnosis (DoH) is a dynamic condition that depends on the balance of stimulation caused by surgery, and the dosage of anesthetics. There are currently over 10 devices on the market that use pEEG to monitor DoH.[4]

1.3.1 Signal Processing

Currently available devices mainly record electrical brain activity using forehead electrodes. The received signal at the skin's surface is very small (approximately 100 times smaller than electrocardiographic ones) and therefore very sensitive to perturbations. Amplification and subsequently filtering of the raw signal are needed to remove artifacts and allow further signal processing. As a next step, an analog-to-digital converter (ADC) divides the continuous signal into time periods and converts it into a discrete signal. The conversion from analog to digital signal results in a loss of fidelity. Further filtering is performed to extract the desired data before complex mathematical manipulation calculates the DoH indices. Some monitors isolate the higher frequent electromyogram (EMG) and display it as a separate DoH indicator. The algorithms for most commercially available DoH monitors are proprietary.[4,12]

1.3.2 Signal Analysis Methods

DoH monitors convert the complex EEG signal into a dimensionless number, the DoH index. Therefore, the raw digitalized EEG signal undergoes mathematical and statistical modeling to determine a final DoH index. The BIS monitor, the current market leader, uses the characteristic changes in EEG, from small amplitude and fast frequencies towards larger amplitudes and slower frequencies, as depth of anesthesia deepens (Figure 1). It stands to reason, to have a closer look at the BIS index in order to understand the basic concept of DoH indices. Most other DoH monitoring devices (except for evoked potential monitors) follow a relatively similar approach. The BIS is a dimensionless number from 0-100 with values close

to 100 denoting an awake state, while 0 represents a flat EEG (isoelectricity). The recommended target range for general anesthesia is a BIS value between 40 and 60.

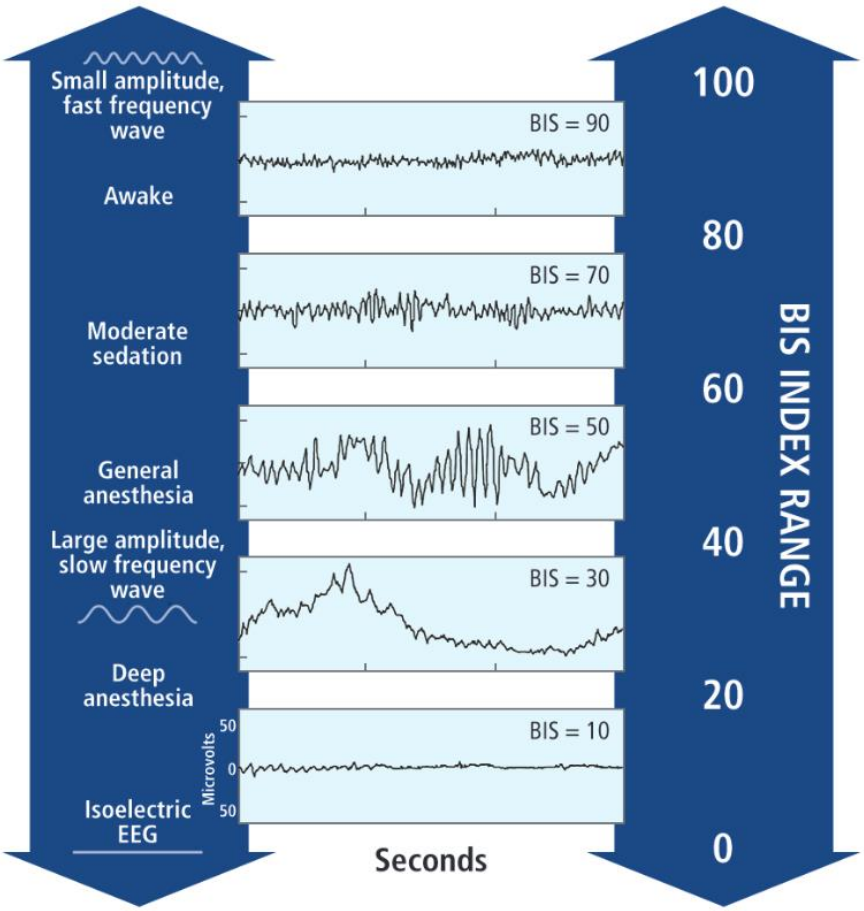

Fig. 1: BIS scale from 0 (flat EEG) to 100 (awake) and typical correlating electroencephalography *(*EEG) recordings. In general, amplitude increases and frequency decreases for deeper stages of anesthesia. The recommended range for general anesthesia ranges from 40 to 60. Figure from Kelly *et al.*[13]

The DoH index of other devices usually follows a similar concept but different preprocessing and data analysis techniques are implemented to extract the relevant information of the signal. Signals are analysed in both, time, and frequency domain.

1.3.2.1 Time Domain Analysis Methods

The signal, as a function of time, is used to detect burst suppression, an EEG pattern linked with deep states of general anesthesia. The conventions for computing BSR are chosen empirically and differ for each monitor in voltage threshold, minimal isoelectric (suppression) time, and overall length of time period over which BSR is computed.[9]

1.3.2.2 Frequency Domain Analysis Methods

Frequency domain analysis is a powerful tool that allows us to present complex biosignals as a function of frequency and extract the sections of interest. Fast Fourier Transformation (FFT) is a mathematical technique that rapidly decomposes a function of time into the frequencies that constitutes it. EEG, as a function of time, is decomposed into its individual sinusoidal components with different frequencies, amplitudes, and phase shifts. An analogy is white light (raw EEG) that is decomposes into a spectrum of separate colors (frequencies) with different intensities (amplitudes) by passing a prism (FFT).

Bispectral Analysis is a higher-order mathematical manipulation used to quantify nonlinear relations between two component EEG frequencies *f1* and *f2*. The FFT of both frequencies (*f1* and *f2*), and their frequency sum (*f1+f2*) are multiplied to determine the bispectral magnitude with high values indicating correlation between those component frequencies. Additionally, biocoherence describes the degree of phase coupling between *f1*, *f2* and *f1+f2*.

1.3.2.3 Entropy

Originally derived from thermodynamics, entropy has been successfully applied to information theory by Shannon Weaver and later to signals by Johnson and Shore.[14] In the context of EEG entropy describes the irregularity, complexity, and unpredictability characteristics of signals. With increasing anesthetic concentrations, irregularity and randomness of the waveforms decreases. FFT is used to split the signal in its sinusoidal components and to calculate the power spectrum. Every frequency is then assigned a specific value by applying the Shannon function to the power spectrum. The sum of the spectral values equals the spectral entropy. The variance of the spectral values decreases with increasing DoH.[14,15]

1.3.2.4 Auditory Evoked Potentials

Auditory evoked potentials (AEPs) provide a method to test the neural pathway carrying information from cochlea, inside the ears, to cortex, which is a part of the brain that plays a key role in consciousness. AEP reflect time-locked EEG responses to repetitive auditory stimulation, usually delivered as clicks through headphones. The corresponding mid-latency AEP (MLAEP) waveform is detected and isolated from background EEG signal

utilizing its time-locked properties. The MLAEP response changes predictably with increasing concentrations of inhaled and intravenous anesthetic drugs. More precisely, latency increases while the amplitude decreases with deepening stage of hypnosis. This is the basis for the generation of the dimensionless DoH index using analyzation and classification techniques.

1.3.3 Currently Available Devices

The Bispectral Index System Monitor (BIS Monitor; Covidien, USA) was approved by the United States Food and Drug Administration (FDA) in 1996 to measure the hypnotic depth using pEEG. Currently, over 10 pEEG-based monitoring devices are on the market. Examples include, but are not limited to, E-Entropy Module (GE Healthcare, USA), Narcotrend Compact M (MonitorTechnik, Germany), AEP A-line Monitor (Danmeter, Denmark), SEDLine Monitor (Masimo, USA), and NeuroSENSE (NeuroWAVE, USA).[4] Table 1 shows examples of available monitors. In general, all monitors simplify the raw EEG into a dimensionless DoH index. Most of the indices are empirically calibrated numbers derived from adult EEG database that correlates with a clinically observed depth of sedation. One exemption is the NeuroSENSE monitor, which mathematically derives its DoH index. The main differences between the monitors lie in the EEG data selection criteria, the filtering, and data analysis techniques. It is common practice in the industry that the algorithms remain proprietary and confidential.

Table 1: Examples of Currently Available Processed EEG-Based Monitors in Alphabetical Order.

Device	DoH Indices and Range	Other Parameters	Algorithm Description
AEP Monitor/2 (Danmeter A/S, Odense, Denmark)	AAI: 0-100	BSR, EMG	AAI is based on MLAEP and EEG signals. For deeper states of anesthesia MLAEP signals are low in quality and EEG-based spectral analysis is given more weight
BIS Monitor (Medtronic, Minneapolis, MN)	BIS: 0-100	BSR, EMG	BIS algorithm based on power spectral analysis, bispectral analysis, and burst suppression data.
Entropy Module (GE Health care Technologies, Helsinki, Finland)	SE: 0-91 RE: 0-100	EMG	SE is computed over EEG dominant part of spectrum (0.8–32 Hz). RE includes the higher frequent EMG dominant part (0.8–47 Hz). Both are calculated using spectral entropy (power spectral analysis and the application of the Shannon function).
Narcotrend Monitor (MonitorTechnik, Bad Bramstedt, Germany)	stage: A-F index: 0-100	EMG	Burst suppression, time and frequency domain analysis
NeuroSENSE Monitor (NeuroWave Systems Inc, Cleveland Heights, OH)	WAV_{CNS}: 0-100	BSR, EMG	Wavelet analysis of the EEG signals in time and frequency domain
SEDline Monitor (Masimo, Irvine, CA)	PSI:0-100	DSA	Frequency analysis of the 4-channel EEG incorporates power, power gradients, and covariances among regions (anterior–posterior relationships and coherence between bilateral brain regions).

Abbreviations: AEP, auditory-evoked potential; BSR, burst suppression ratio; DSA, Density Spectral Array; EEG, electroencephalogram; EMG, electromyogram; MLAEP, middle-latency AEP; PSI, Patient State Index; RE, response entropy; SE, state entropy. Adapted from Fahy and Chau[4]

1.4 EEG Signatures of Traditional Anesthetics

Propofol, the most commonly used hypnotic agent for total intravenous anesthesia (TIVA), is linked to characteristic changes in EEG pattern during anesthesia. Generally, an increase in low frequency EEG power (<1 Hz) and prominent frontal alpha oscillation (8-12 Hz) with alpha peaks in both power, and biocoherence spectra, with average frequencies of 10.6 Hz and 10.7 Hz, respectively have been linked to propofol-induced unconsciousness.[16,17] Similar EEG patterns can be observed for inhaled ether-derived anesthetics such as sevoflurane, isoflurane, and desflurane. Overall a shift towards slower EEG frequencies, reduced neuronal activity, and increases synchrony is associated with deepening of anesthesia.[4]

1.5 Introduction to Ketamine

Ketamine, uniquely combines analgesic, hypnotic, and amnesic properties without depressing the respiratory and cardiovascular system. Expected hemodynamic or cardiac instability such as in trauma surgeries, and reactive airway diseases such as asthma are clinical indications for the use of ketamine.[18,19] Moreover, ketamine is the anesthetic of choice in combat medicine due to its wide safety margin and often limited access to ventilation, and clinical and instrumental monitoring. In addition, ketamine has shown to be a potent adjuvant to multi-modal anesthesia and is suspected to significantly improve post-operative pain management. Multi-modal anesthesia combines the effectiveness of several agents in optimal dosage to maximize efficacy while minimizing side effects. Rèmerand *et al.* found that a ketamine bolus at the beginning of surgery, followed by a 24 hour infusion, not only reduced morphine consumption after surgery but moreover decreased postoperative chronic pain.[20] However, the knowledge of the effects of ketamine on EEG and consequently pEEG is limited.

Ketamine binds preferably to N-methyl-D-aspartate (NMDA) receptors on inhibitory interneurons in the cortex, limbic system (amygdala), and hippocampus. The opposing interaction of excitatory and inhibitory interneurons is responsible for whether information is transmitted any further. Ketamine, an NMDA antagonist, blocks the receptor of the inhibitory interneurons, which leads to an uncoordinated increase in neural activity and an active EEG pattern – contrary to other anesthetic agents.[1] The maximal effect of ketamine on EEG was reported to occur at 2-10 minutes after administration.[21] Characteristically, anesthetics shift power towards the lower frequencies. Low dose ketamine, in contrast, introduces fast oscillation in high β- and low γ-range (24-32 Hz).[22] Other studies associate ketamine anesthesia with increased γ- (32-100 Hz) and δ-power (0.1-3 Hz).[23] Koch *et al.* reported a dose-dependent decreases in α-activity (8-12 Hz) and increase in θ-power (4-8 Hz) as a consequence of ketamine administration. Ketamine shifts the propofol induced α-peak from 11 to 14 Hz in both power and bicoherence analyses.[17] It is thus not surprising that pEEG parameters used in DoH monitor algorithms may also be affected by ketamine. Conflicting results have been reported for some of the DoH indices. Hayashi *et al.* found a significant increase of the BIS value following ketamine administration.[17] Yet, no significant change in the ketamine group was reported for A-Line auditory evoked potential index, and Bispectral

Index by Vereecke *et al.* , while state and response entropy increased.[24] Maksimow *et al.* concluded that the Entropy module, while adequate for propofol, is not suitable for assessing the depth of ketamine anesthesia.[25]

1.6 Aim of this study

Monitoring brain activity provides the anesthesiologist with valuable feedback on the patient's level of anesthesia and may reduce the risk of incorrect dosage. DoH monitors potentially reduce drug consumption and recovery time; enabling a more cost-efficient sedation and quicker recovery for the patient.[26,27] Certain anesthetic drugs such as ketamine are suspected to paradoxically modify the DoH index values. As of now, no attempt has been made to compare different DoH monitors in the presence and absence of ketamine. The aim of this study is to answer two closely linked research questions.

First, does the presence of ketamine affect the DoH output of three commonly used depth of monitors (BIS, Entropy, and NeuroSENSE)? BIS and M-Entropy are two of the most commonly used monitoring devices for DoH, and the NeuroSENSE device was selected as it was used to record the data and has been designed to be used in closed loop anesthesia.

Second, how do these monitors differ in their behavior when ketamine is present? While DoH scales are not standardized, the manufacturers of all three monitors recommend an appropriate depth of general anesthesia values between 40 and 60, allowing some comparison.

We used a replay system which enables replay of EEG from previously recorded cases to all three monitors. This allows us to overcome monitor variability which is difficult to test *in vivo* because only one set of monitor electrodes can practically be placed on the forehead of a patient while adhering to manufacturer recommendations. We propose a safe, reproducible, easy to use, and low-cost method to explore differences between these three monitors in the presence and absence of ketamine, and gain more information on the clinical question of how ketamine affects pEEG indices.

CHAPTER 2

METHODOLOGY

The following section is intended to provide an overview of the methods used to collect and analyze the data of this study. First, it covers the verification process of the developed replay system, and how the source data were obtained. Second, it introduces the hard- and software used to collect the data, the study design, and the analysis methods applied to the replayed data.

2.1 Replay System

The replay system, as the central piece of this study, is composed of a slightly modified USB/audio interface U-PHONO UFO202 (Behringer, Willich, Germany). In its stereo output mode, it is essentially a high fidelity, 16-bit digital-to-analog converter (DAC). Its main benefit is that it provides a low cost method to precisely replay audio signals. Besides the exact timing, a faithful replay of the clinically relevant frequency range for EEG (0.1-50 Hz) was important to the success of this study. Before replaying the audio signal to the monitors they had to be scaled down to the EEG-typical micro voltage range. This was accomplished by sending the signal through a voltage divider (approximately 1:10,000).

2.1.1 Hardware and Modifications

Previous data show that the replay system lacks low-frequency fidelity whereby essential frequencies during anesthesia are attenuated by the built-in high-pass filter. To improve the low-frequency fidelity we replaced the integrated 22 µF capacitors in the high-pass filter of the final stage of the circuit board with 1,000 µF capacitors.
The high pass filter cut-off frequency f_C is determined by:

$$f_C = \frac{1}{2\,\pi R\,C}$$

When the resistance value R is held constant the cut-off frequency is inversely proportional to the capacitor value C. Thus, if the capacitance is increased by the factor

$$k = \frac{C_{1000}}{C_{22}} = \frac{1{,}000\mu F}{22\mu F} = 45.45$$

the cut-off frequency will be decreased by the same factor k = 45.45. The new cut-off frequency (f_{C1000}) can be determined by:

$$f_{C1000} = \frac{f_{C22}}{k} = \frac{1}{2\,\pi R\; C_{22} * k} = \frac{1}{2\,\pi R\; C_{1000}}$$

2.1.2 Verification

We verified the replay system in two steps. First, using a sine wave, whereby a stepwise decrease in frequency from 50 Hz to 0.1 Hz, in 0.1 Hz steps, was used to quantify the clinically relevant frequency range. Both channels were independently calibrated at a sine wave of 10 Hz (no damping) in order to faithfully reproduce a peak-to-peak amplitude (Vpp) of 100µV. A variance of less than ± 5% for both frequency and amplitude (Vpp) was considered to be acceptable. We expect to see damping around the 0.5 Hz and 50 Hz frequencies due to built-in filters in the NeuroSENSE monitor. Second, we replayed both synthetic and previously recorded EEG signals to the NeuroSENSE monitor, the same model of monitor that originally recorded the signal. The output triplet of DoH indices (in both cases WAV), EMG, and BSR were visually aligned and compared in the time domain. The Bland-Altman method was used to compare the two measurements of both DoH indices.

2.2 Data Set

With Fraser Health research ethics board approval [FHREB 2016-054] our team previously conducted a randomized, open label study to collect EEG data from 30 adult patients (age 18-54) undergoing total intravenous anesthesia with propofol and remifentanil in the presence of ketamine (NCT02908945). Participants were randomized to one of the three groups:

I) Group 0.5 (G 0.5) received 0.5 $mg \cdot kg^{-1}$ ketamine bolus, followed by a 10 $mcg \cdot kg^{-1} \cdot min^{-1}$ infusion
II) Group 0.25 (G 0.25) received 0.25 $mg \cdot kg^{-1}$ ketamine bolus and a 5 $mcg \cdot kg^{-1} \cdot min^{-1}$ infusion
III) Control (Ctrl) group received no ketamine

EEG data was collected using the NeuroSENSE monitoring system. Anesthesiologists were blinded to the DoH index (WAV), but not to the administered dose of ketamine. The NeuroSENSE monitor formatted each case at sampling frequency of 256 Hz per the European Data Format (.EDF). Through close contact with the device manufacturer, we were able to extract a less-processed signal at a higher (900 Hz) sampling rate in .PKT format, a binary data format with data from each channel preceded by a header.

2.3 Study Design

This study was authorized through both the original research ethics board (REB) approval, which covered the secondary analysis of the collected EEG data, and a second REB approval for DoH replay to enable DoH monitor comparisons. The previously collected data from the ketamine study, in its .PKT format, served as source data of this study and were subsequently replayed to the BIS, Entropy and NeuroSENSE DoH monitors. As part of the preprocessing, the data were converted into text files (.txt) via an in-house developed application and subsequently transformed into audio files (.wav) using MATLAB (MathWorks, Natick, MA). For replaying the audio files we used version 2.1.3 of the open source software Audacity® (The Audacity Team, Pittsburgh, PA) recording and editing software. [28] For all three monitors we recorded the DoH indices, BSR, and EMG values, except for the Entropy monitor, which does not calculate EMG parameters (Figure 2).

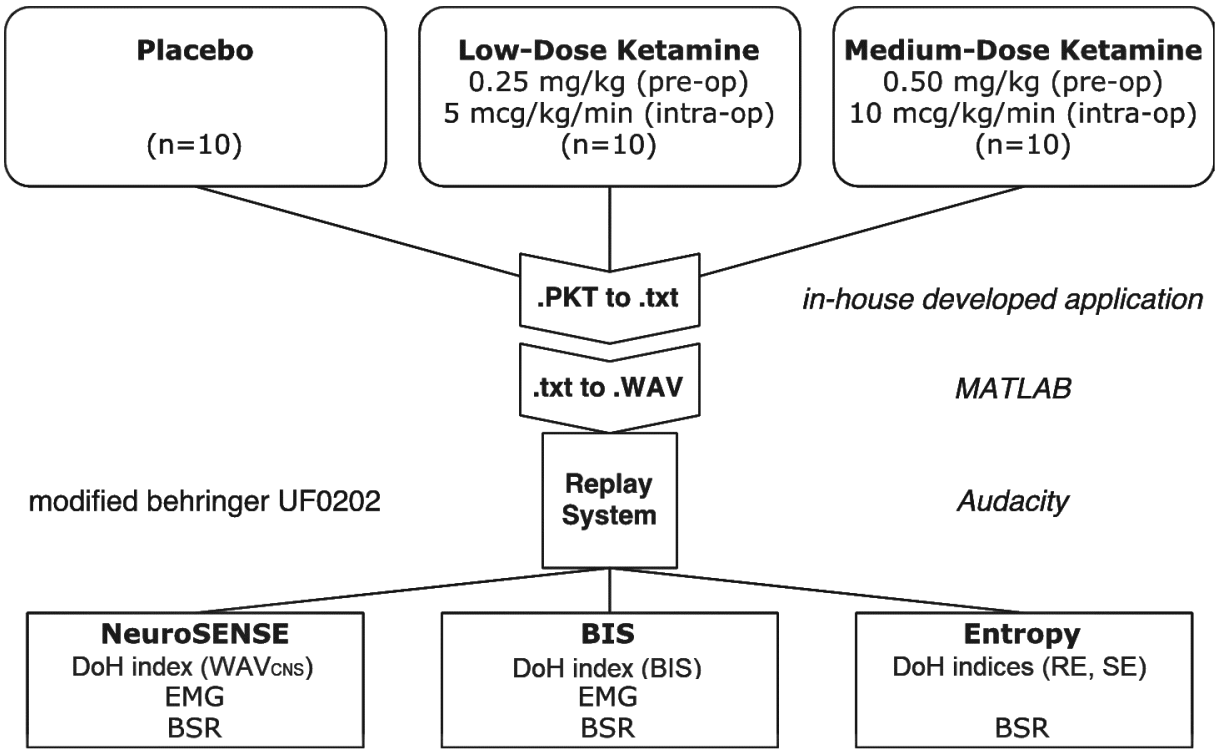

Fig. 2: Flow chart of data replay system used. Steps included data source (top), file processing from raw data to replayed data, including used hardware (left) and software (right) tools employed, and DoH monitors used for data collection as well as variables recorded (bottom).

Time-alignment of the cases was needed to allow performance comparison between the devices, emulating their parallel data capture from the same patient. Previous test had shown that a 'cold' start from isoelectric EEG caused difficulties for some DoH monitors (particularly the BIS), which made an alignment at the start of each case unfeasible. Thus, we inserted one minute of synthetic "awake" EEG at the beginning of each case to allow the DoH algorithm for each monitor to stabilize; this section was subsequently removed in the alignment process. We decided to align the collected parameter triplets at the end of each case using the first derivative of the BSR signal. The final drop to isoelectric EEG at the end of each case recording, when the electrodes are removed, is detected as a rapid BSR increase. Ten percent of the cases required manual alignment (case 12, 14, and 18) due to incomplete recordings or invalid (NaN) values of the BSR in one of the three monitors. With the alignment at the end of each case the expected monitor-specific delays will be maintained. It should be noted, however, that the downstream monitor-to-monitor discrepancies will reflect the delays between the different devices in addition to the effect caused by ketamine.

2.4 Data Analysis

DoH indices were compared during the surgical preparation phase (first 15 minutes of each case), in which peak ketamine DoH effect (between minute 2 and 10 after administration) was expected to be observed,[21] and also as the absence of surgical stimulation reduced noise. Data were summarized as median [Q_1, Q_3] using MATLAB, unless otherwise specified. All comparisons were performed using median differences (MD) and their 95% confidence interval, and p-values using Wilcoxon rank-sum test in MATLAB. The significance level was set at α=0.05. Multiple comparisons were accounted for with Bonferroni correction. This was achieved by dividing the critical α by the number of comparisons (n) e.g. n = 2 for the two ketamine groups compared to placebo, an n = 3 for the monitor comparison of the three devices. For each ketamine dose DoH indices were analyzed in 30 seconds intervals and displayed as a combination of violin and boxplots, grouped by monitors. The violin plot complements the boxplot by displaying the distribution of the raw data using kernel density estimation. The kernel density bandwidth was set to one for all plotted figures to ensure a fair visual comparison. For easier abstraction of key values, median values (Q_2) and interquartile range (IQR), which describes the difference between the upper (Q_3) and lower quantile (Q_1) were overlaid as box plots for each monitor, again grouped by ketamine dose. The values were calculate over 30 second time windows for the first 15 minutes of each case.

Subsequently, DoH indices were analyzed at minute 1, 5, 10 and 15 and displayed as a combination of violin and boxplots. The reference period was fixed as the minute prior to the first indication of a fast decrease in DoH upon induction of anesthesia. Differences were calculated over a 1 minute window, ending at 1, 5, 10, and 15 min, respectively. The data were used to perform a comparison between drug dosages within each monitor, to investigate the effect of ketamine on DoH indices. For each monitor, median DoH differences between the two ketamine groups and the control group were plotted as boxplots and compared using Wilcoxon rank-sum tests before induction at minute 1 and after induction at minute 5, 10, and 15. Subsequently, the data were rearranged to enable monitor comparison within each dosage group, to explore differences between monitors in the presence and absence of ketamine. For each ketamine dose, DoH differences between the monitors were plotted as boxplots and compared using Wilcoxon rank-sum tests. For all boxplots the MATLAB default whisker setting (w = 1.5 IQR) was used. Data points greater than

$$Q_3 + w \times IQR$$

or less than

$$Q_1 - w \times IQR$$

were considered to be outliers.

Bland-Altman analysis offers a simple yet conclusive method of quantifying the agreement between two methods of measurement by exploring the differences[29]. We used a heatmap version to graphically represent the relative frequency of a value within a data set. The more frequently a value occurs, the darker it is represented in the graph using a log-transformation. The DoH difference (error) and 95% limits of agreement (2 SD) were overlaid for each comparison. Thus, pairwise comparisons of BIS vs. ENT, BIS vs. NS, and ENT vs. NS devices were performed for the surgical preparation phase (first 15 minutes of each case).

CHAPTER 3

RESULTS

The results of the replay system's verification and modification, relevant study results from the previous ketamine trial, and the results of this study are presented in this chapter.

3.1 Replay System Modification

The capacitor replacement resulted in a clear improvement of the low frequency performance. This improvement allowed us to replay frequencies from the lower frequency bands within the bandwidth of the NS monitor, which ranged from 0.5 Hz to 50 Hz (Figure 3).

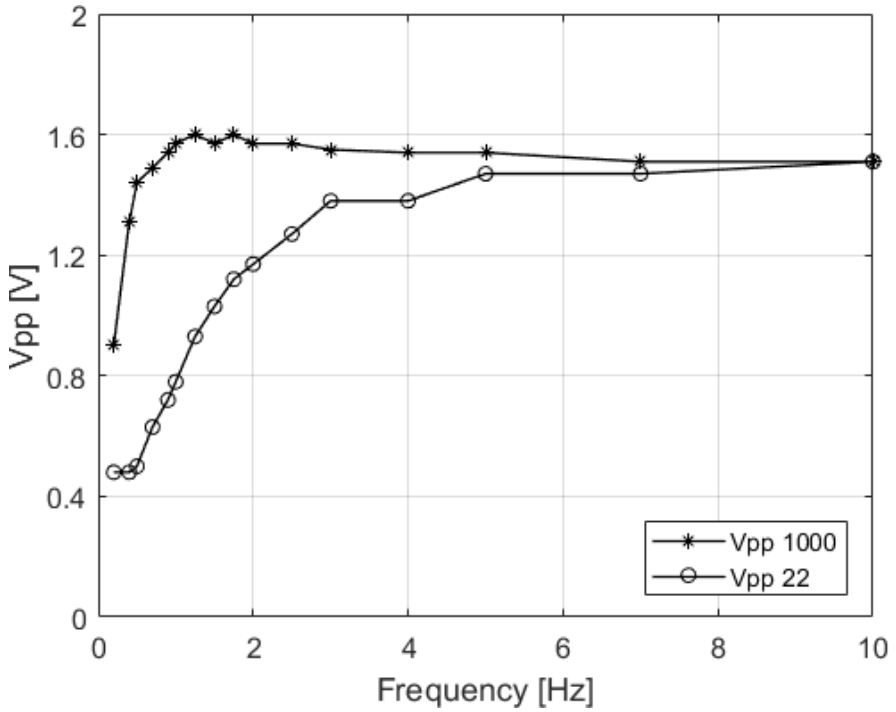

Fig. 3: Low frequency amplitude behavior of original and modified audio board. The modified audio board (Vpp 1000) shows significant better low frequency behavior due to the replacement of a 22 µF capacitor with a 1000 µF one. The remaining drop in amplitude for very low frequencies can be tolerated because of the integrated NeuroSENSE's high pass filter at a cut-off frequency of 0.5 Hz.

3.2 Replay System Verification

The frequency and amplitude ratio was calculated by comparing the original signal ($Vpp_{original}$ = 100 µV, and $f_{original}$ = (50 – n × 0.1) Hz for n = 0 to 499) to the replayed one.

$$Vpp_{ratio} = \frac{Vpp_{replayed}}{Vpp_{original}} \; ; \; f_{ratio} = \frac{f_{replayed}}{f_{original}}$$

Vpp_{ratio} and f_{ratio} remained within the accepted ± 5 % tolerance limits for high frequencies with medians [Q_1, Q_3] of 100.02 [98.83, 100.39] % for the amplitude and 99.99 [99.94, 100.01] % for frequencies between 50 Hz and 2.6 Hz (Figure 4). While frequency was preserved for high frequencies, a frequency-dependent decrease of up to 3 % for the amplitude behavior was detected for increasing frequencies. The expected damping around 0.5 Hz and 50 Hz is due to the built-in filters of the NeuroSENSE monitor, which caused a decrease in amplitude. Untypically for damping, the frequency increased slightly for low frequencies; this can be explained by fewer oscillations per period for low frequencies consequently less accuracy in the measurement when calculating the frequencies using MATLAB. Furthermore, we found that the actual sampling frequency of our NeuroSENSE monitor at 265 Hz nominal to be 256.021 Hz. After confirming the observation with the monitor manufacturer, we accounted for this discrepancy in further analysis.

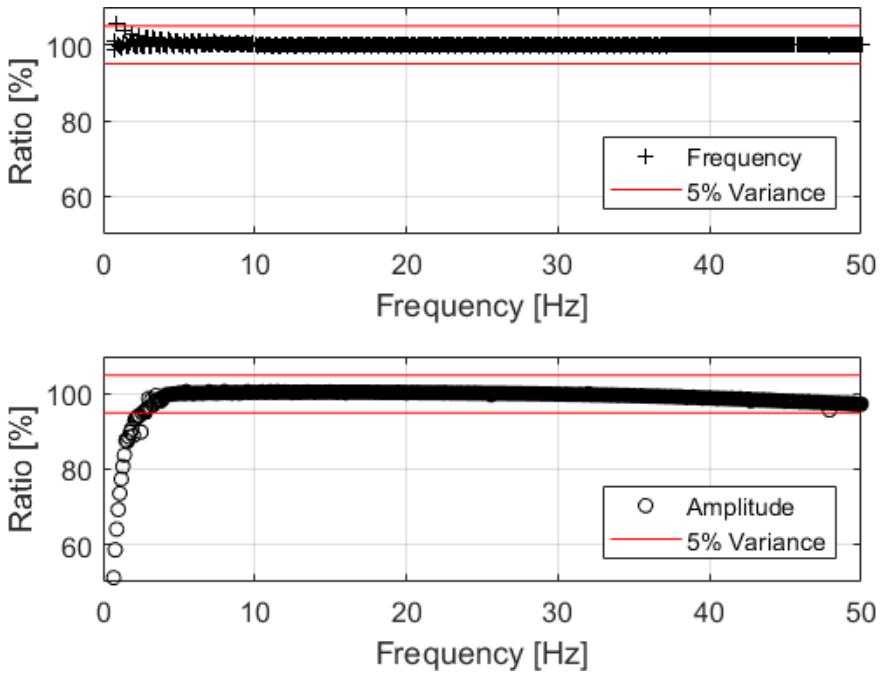

Fig. 4: Frequency and amplitude ratio of original to replayed signal calculated over a stepwise decreasing sine wave with a frequency range of 50 Hz to 0.1 Hz and the ± 5 % limits (red). While frequency was preserved for high frequencies a frequency-dependent decrease up to 3 % for the amplitude behavior was detected for increasing frequencies.

Replaying one case back to the same monitor resulted in clearly correlated signals, which can be seen in the time-synchronized overlap of the original and the replayed signal for all three parameters (Figure 5). Case 10 was chosen because of its short duration and the presence of BSR. The Kendall's τ correlation coefficients calculated using MATLAB were τ_DoH=0.77, τ_EMG=0.50, and τ_BSR=0.94. The correlation between the DoH indices is higher during intervals without burst suppression (τ_DoH=0.85 for the first 17 minutes).

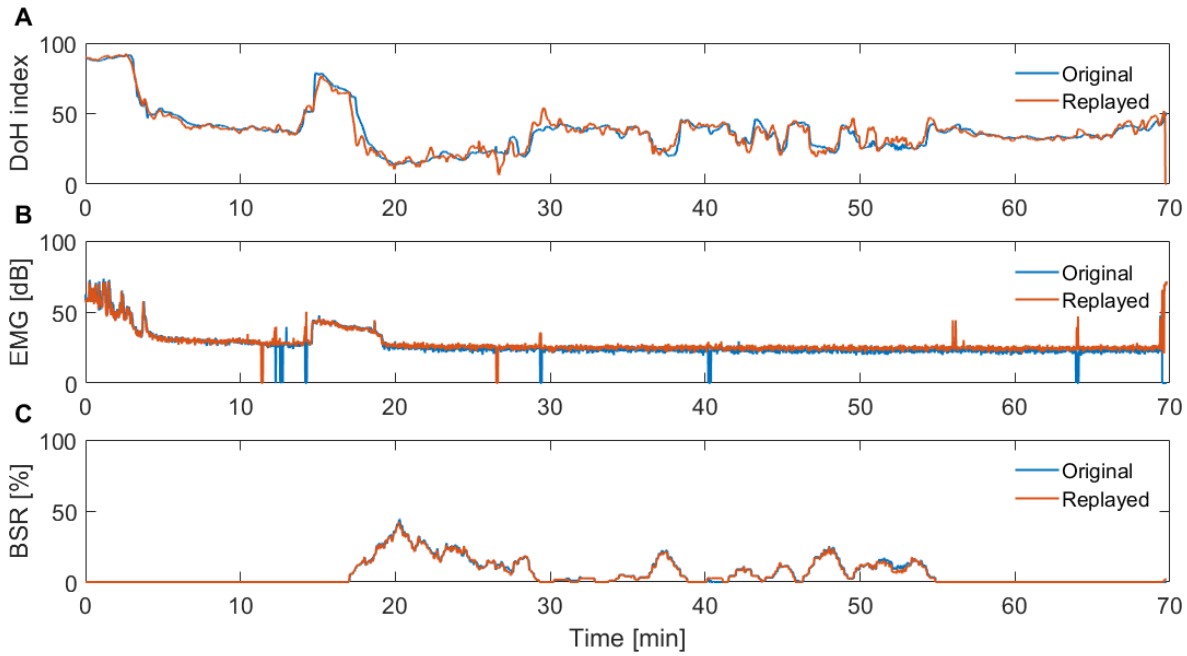

Fig. 5: Comparison of time-synchronized pEEG parameters (A: WAV, B: EMG, and C: BSR) of original (blue) and replayed (orange) EEG signal for one sample case.

The Bland-Altman analysis of the DoH indices resulted in an equal distribution of WAV differences throughout the full DoH range of the same case which indicates the absence of systemic differences between the original and the replayed case. This was quantified by a root mean squared error (RMSE) of 0.041 with a standard derivation (SD) of 4.407 for the duration of the entire case. However, 95 % of the replayed values differ by a maximum of ± 8 DoH units from the original case (Figure 6). This is surprisingly high and may be caused by timing issue or perturbations affecting the replayed signal. This will be further addressed in the limitations section in chapter 4.

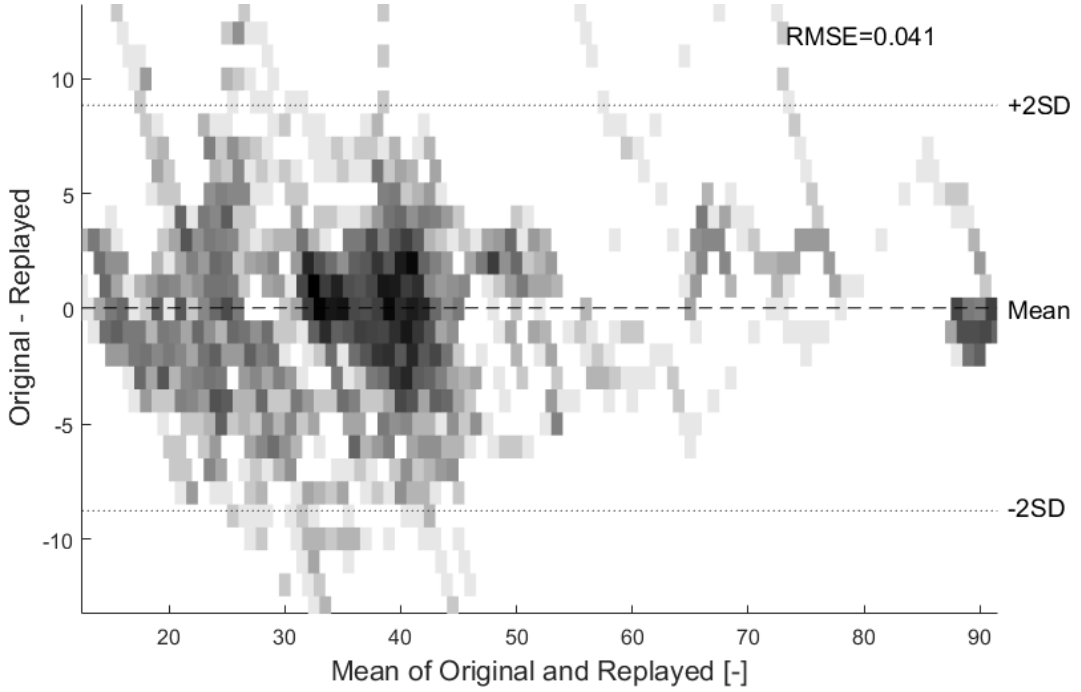

Fig. 6: Bland-Altman comparison of original and replayed to the NS monitor WAV index for one sample case. Data is equally distributed throughout the range. 95 % of the replayed WAV values differ by maximum ± 8 DoH units (± 2SD) to the original case.

3.3 Study Results

Three cases, one of each group, had to be excluded from further analysis. Case 1 received a double dose of ketamine (a protocol violation), case 4 was excluded for ethical reasons (the patient didn't consent to the use of their data for secondary analyses), and case 7 had to be removed due to incomplete recording of the induction phase (due to a technical failure). Ultimately, data from 27 cases, 9 from each the group [G 0.5, G 0.25, and Ctrl], were available for data analysis.

In our previous study, the propofol induced α-spindles (peak 8–16 Hz) were shown to be shifted to higher frequencies in the normalized EEG power plots (Figure 7). Furthermore, we identified an increase of the normalized power in the β- (16–32 Hz) and γ-band (32–64 Hz). These observations were consistent with previous reports.[17,22] This finding is important for the interpretation of the results and therefore re-stated here.

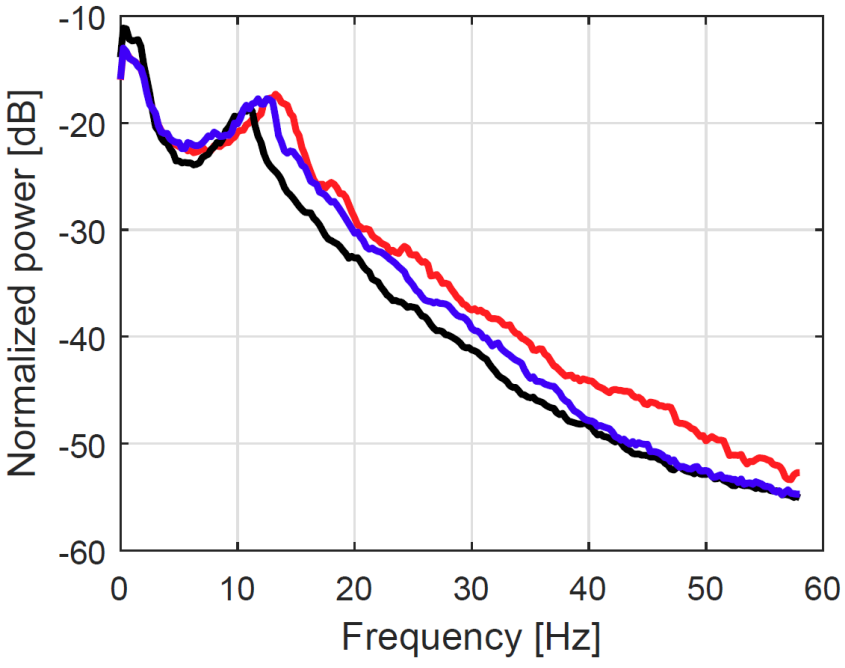

Fig. 7: EEG power, normalized over the 0-64 Hz frequency range, at 5 min after the start of propofol infusion for G 0.5 (red), G 0.25 (blue) and the Control group (black). Figure from van Heusden *et al.* [29]

The distribution of the raw data was graphically represented using violin plots. Control group showed a multimodal distribution in the induction phase between minute 3 and minute 6 (Figure 8C). Hence, patients were classified either awake with DoH indices greater than 75 or anesthetized with DoH values below 60. This two-stage distribution was observed across all monitors, but it was particularly distinguishable for WAV indices. This trend did not appear in cases in which ketamine was administered.

In G 0.5 between minute 5 and 15, BIS, SE, and WAV values exceeded the 40-60 range associated with adequate anesthesia for median 100 % and 55 %, and 95 % of the time, respectively. In G 0.25 BIS, SE, and WAV values were greater than 60 for 75 %, 50 %, and 50 % of the time. In the Control Group this only applied to 10 %, 5 %, and 5 % of the BIS, SE, and WAV values, respectively. The Control Group in which the DoH indicated relatively deep anesthesia, with a median of 52.4 [45.6, 58.0], 40.0 [35.0, 45.0], and 44.5 [40.0 48.3] for BIS, SE, and WAV.

Observed SR values were relatively small and we therefore decided to present them qualitatively. We reported the presence of SR values for each 30 seconds bin in percent. Incomplete recordings or invalid (NaN) values were excluded. The Entropy device solely recorded BSR for the G 0.5 for 2 out of 9 cases. Those values were detected either at the beginning of one case or related to very low DoH indices around minute 8 of another case. The number of cases with BSR was higher for the BIS and NeuroSENSE monitors. BIS device has 3, 5, and 5 out of 9 cases with BSR for G 0.5, G 0.25, and Control. Similarly the NeuroSENSE monitor recorded BSR for 2, 6, and 5 out of 9 patients receiving the G 0.5 dose, G 0.25 dose, and no ketamine, respectively.

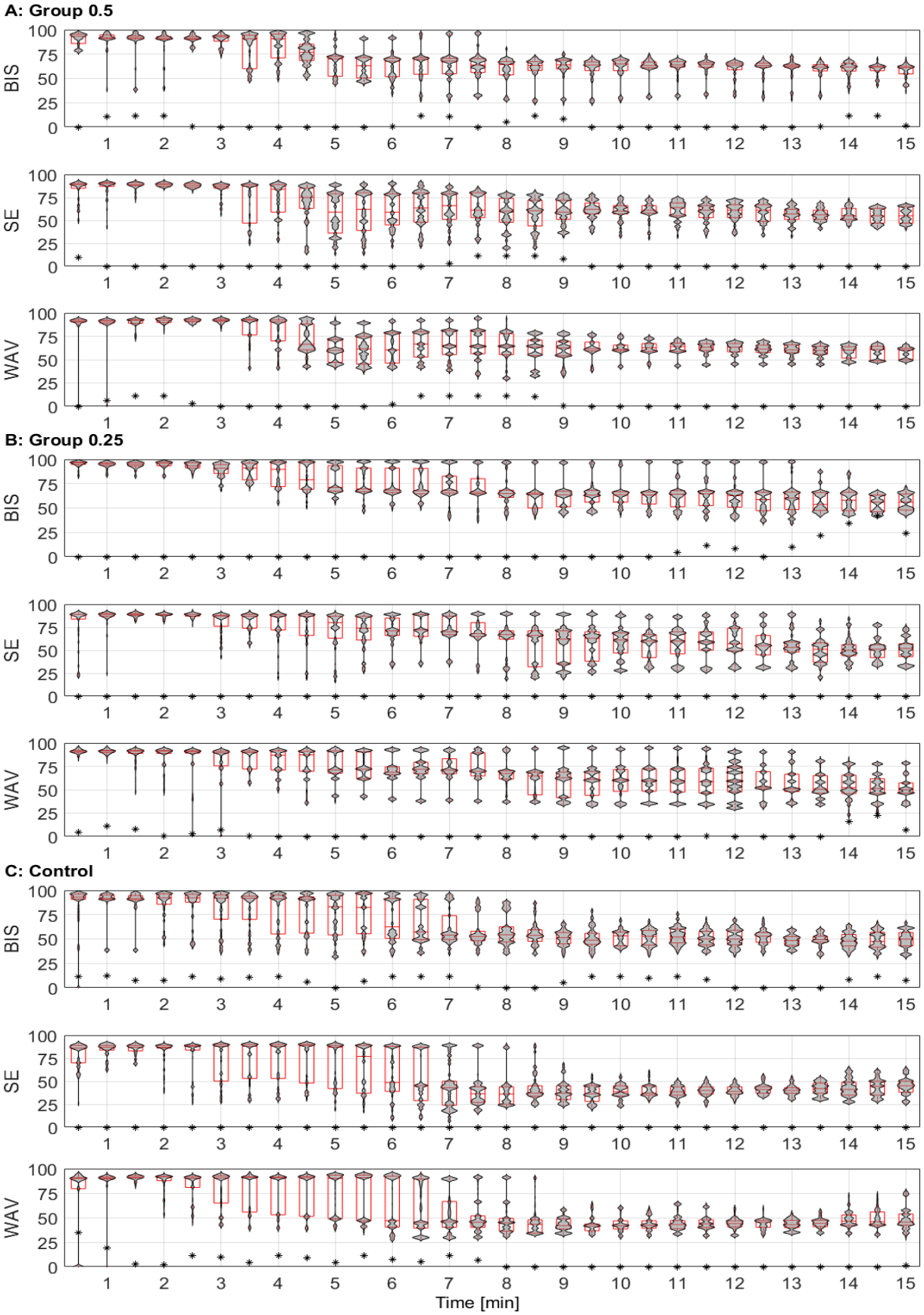

Fig. 8: Combination of violin and boxplot showing DoH indices [BIS, SE, and WAV] for each ketamine dose [A: G 0.5, B: G 0.25, and C: Control] recorded over first 15 min of each case, split into 30 seconds intervals, grouped by monitor specific DoH index. The violin plot illustrates the distribution of the raw data using kernel density estimation (bandwidth = 1 for all plots). Median, Q_1, and Q_3 are represented as red horizontal lines of the boxplot. Percentage of values with BSR in each 30 sec bin is visualized as asterisk.

Both Ketamine groups showed increased DoH indices for all three monitors after induction of anesthesia (Figure 9). The differences between G 0.5 and the control group were highly significant between minutes 9.5 and 13.5 when comparing for WAV and SE indices (both $p<0.005$). DoH indices for the G 0.25 at minute 15 of the case (median [Q1, Q3]) were 56.0 [47.9, 64.5], 52.0 [43.0, 57.0], and 50.0 [46.3, 57.3] for BIS, SE, and WAV respectively. G 0.5 reached median values of 61 [54.6, 62.4], 55 [47, 65], and 60.3 [49.9, 62.1] for BIS, SE, and WAV respectively, at minute 15 of the case. The median value at the same time point for the placebo group were much lower, with 49.9 [43.0, 56.8], 45 [38.0, 50.0], and 45.4 [42.4, 53.8] for BIS, SE, and WAV respectively.

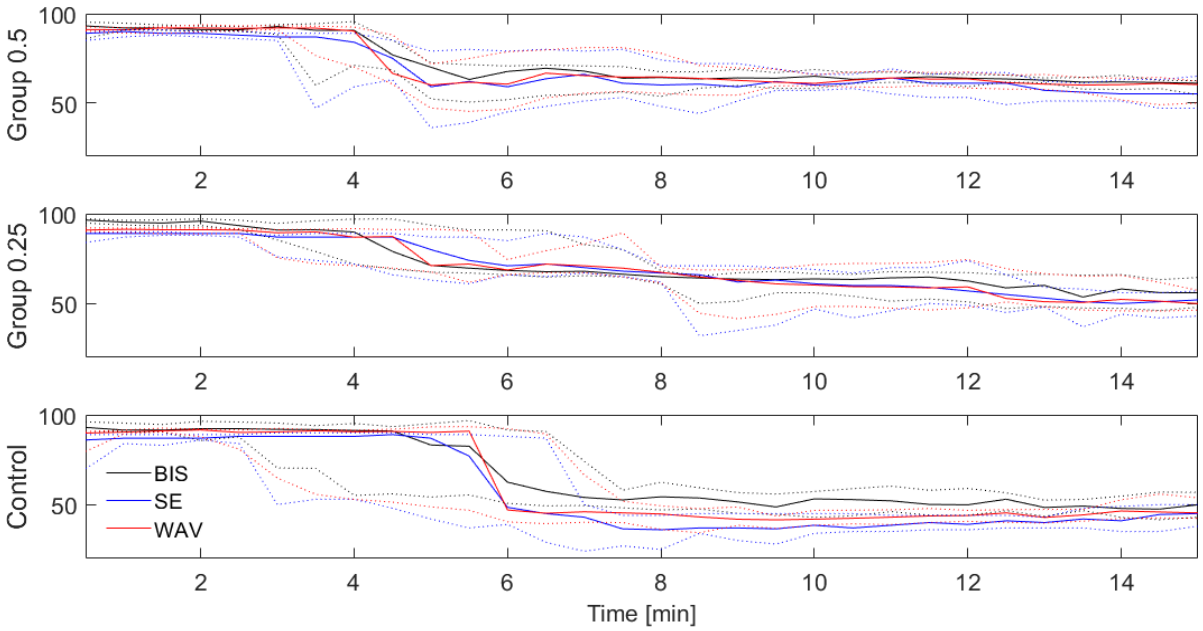

Fig. 9: DoH median values (solid line) and Q_1 and Q_3 quantiles (dotted line) for each ketamine group calculated over 30 second time window for the first 15 minutes of each case, grouped by monitors.

3.3.1 Comparison between Ketamine Groups and Control for each monitor

Comparing median differences (MD) between drug dosages within each monitor, highly significant differences were found in Minute 1, 5, and 10 for both ketamine groups, G 0.25 and G 0.5, for all monitors ($p<0.005$). While the median value in G 0.5 was lower than in the other groups at minute 5 this order was inverted at minute 10 with the highest median values in G 0.5 for all monitors. This trend continued for minute 15 in all monitors, where significant differences between groups was only detected in G 0.5 compared to placebo. This observation applied to all monitors (Figure 10).

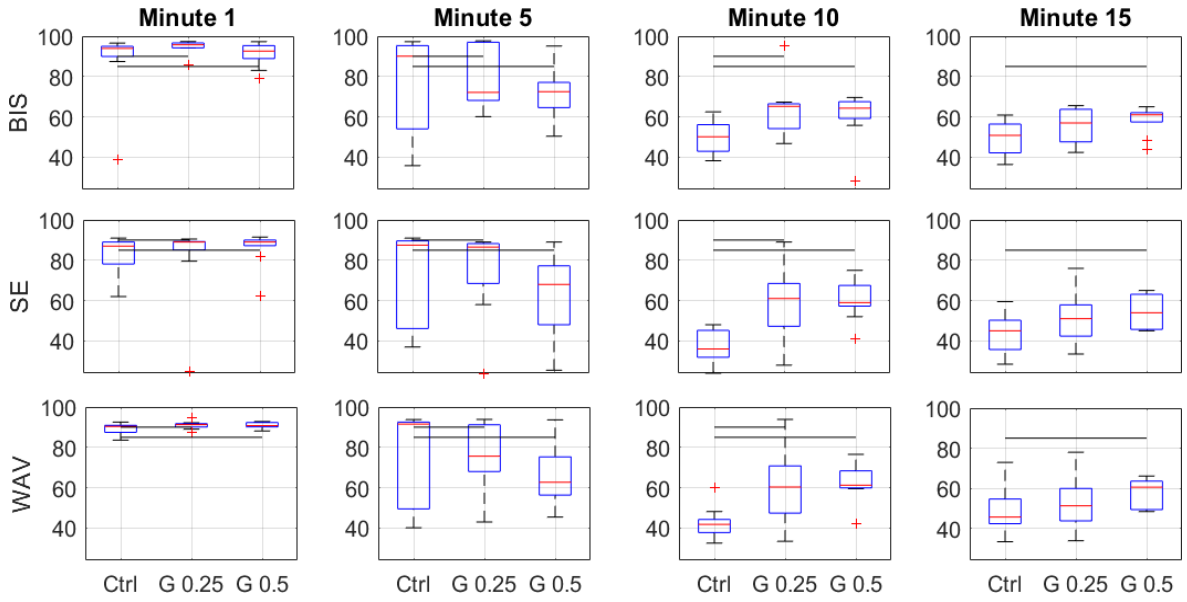

Fig. 10: Median difference between ketamine dosage at minute 1, 5, and 15 for each monitor, showing a combination of boxplot and Wilcoxon rank-sum tests. Highly significant differences ($p<0.005$) between both ketamine groups and the placebo group are presented as black horizontal line linking both groups.

3.3.2 Comparison between Monitors

Comparing MD between monitors within each dosage group, we found no significant differences in either ketamine group after patients were anesthetized (Figure 11). After induction, significant differences were present in the Control group at minute 10 for BIS vs. SE ($p<0.017$), likely due to differences in BSR (see Figure 8C). Significant difference between all monitors were present in minute 1 before ketamine was administered in G 0.25. We found significant differences comparing WAV to SE and BIS (both $p<0.017$). Highly significant differences comparing BIS to SE ($p<0.00\bar{3}$) at the same time window are likely reasoned by the very high BIS median of 95.6 [94.1, 97.1] and the by definition smaller SE range from 0-91.

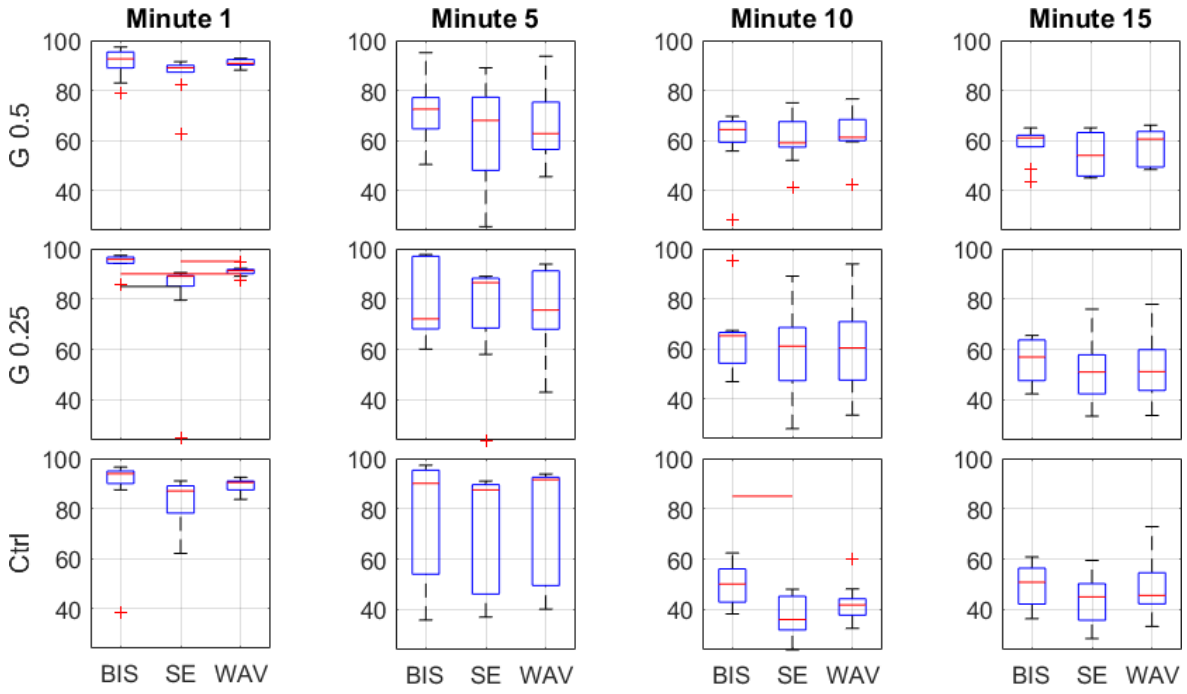

Fig. 11: Median difference between monitors at minute 1, 5, and 15 for each ketamine dose, showing a combination of boxplot and Wilcoxon rank-sum tests. Significant differences between monitors are presented as black ($p<0.00\bar{3}$) or red ($p<0.017$) horizontal line linking both monitors.

3.3.3 Bland-Altman Analysis for Monitor Comparison

The presence of ketamine did not result in a lower agreement between two monitors in neither G 0.25 nor in G 0.5. Comparing BIS to either WAV or SE, the root mean squared error (RMSE) decreased with increasing ketamine dose. For the SE vs. WAV comparison the RMSE was lowest for G 0.25. On average the BIS measured higher values than SE or WAV, which was quantified by a positive error (BIS vs. SE: 2.85, 6.06, and 9.82 for G 0.5, G 0.25, and placebo; BIS vs. WAV: 3.87, and 4.89 for G 0.25 and placebo) except for G 0.5 where the error was -0.29 for the BIS and WAV comparison. The SE vs. WAV comparison revealed that on average the WAV measured 3.1, 2.2, and 4.9 units higher than the SE for G 0.5, G 0.25 and placebo respectively (Figure 12).

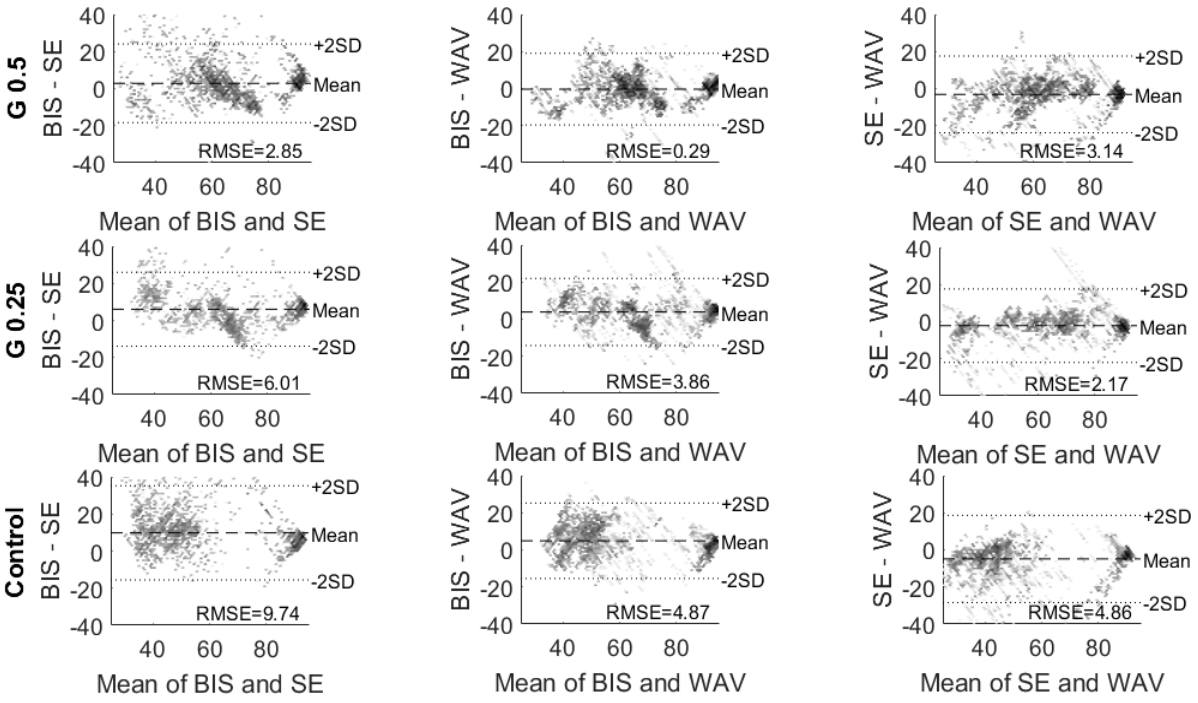

Fig. 12: Bland-Altman comparison for each ketamine group and every possible monitor constellation (BIS vs. SE, BIS vs. WAV, and SE vs. WAV) calculated over first 15 minutes of each case (n = 8,100).

CHAPTER 4

DISCUSSION

This study was designed to answer two questions. First, does the presence of ketamine affect the DoH output of three commonly used depth of monitors (BIS, Entropy, and NeuroSENSE) and second, how do these monitors differ in their behavior when ketamine is present? The study is unique, since to our knowledge no comparison between those three monitors in the presence and absence of ketamine has been performed.

4.1 Ketamine Effect

We found a multimodal distribution in the induction phase of the Control group with no DoH values observed in the light sedation range. Interestingly, both ketamine groups showed a less rapid transition between the two stages with increased DoH values normally associated with light sedation (DoH > 70). Presumed our alignment was performed correctly, this supports the assumption that the ketamine administration leads to an increase in DoH indices, caused by gamma band activity. Hence, when using the DoH indices for feedback during general anesthesia, during the induction phase indices might be increased by the administration of a ketamine bolus, which could possibly lead to overdosing the patient when solely relying on the DoH index for depth of anesthesia assessment. In our previous study[30] we already speculated that the recommended bolus of 0.5 mg/kg of ketamine (G 0.5) introduces a peak in ketamine EEG effect, which exceeds the effect of the corresponding maintenance infusion of 10 $mcg \cdot kg^{-1} \cdot min^{-1}$. This observation needs to be confirmed in a larger study.

Following induction, both ketamine groups showed increased DoH indices for all three monitors, consistent with previous reports.[17,25] The DoH values for G 0.5 were higher than in G 0.25, suggesting a dose-dependent relation. This might make a smaller ketamine dosage more suitable for use during DoH-monitor-guided anesthesia. Analgesic effects of a lower dosage will have to be evaluated.

Between minute 5 and 15, at the beginning of the maintenance of anesthesia, median DoH indices calculated over 30 sec time windows were higher in the presence of ketamine than in the control group. Here, median BIS, SE, and WAV values exceeded the 40-60 range

associated with adequate anesthesia for 100 % and 55 %, and 95 % of the time, respectively in G 0.5. In G 0.25 BIS, SE, and WAV values were greater than 60 for 75 %, 50 %, and 50 % of the time. In the Control Group this only applied to 10 %, 5 %, and 5 % of the BIS, SE, and WAV values, with all of these values at the beginning of the maintenance phase, respectively. Likely, this increase in DoH indices was caused by the increased power in the high frequency gamma band. This finding was backed through the monitor-wise comparison of each ketamine dosage to placebo; DoH indices in G 0.5 were significantly higher at all time points (minutes 1, 5, 10, and 15) for all three monitors ($p<0.005$). In G 0.25, DoH indices were significantly increased in minutes 1, 5, and 10 for all monitors ($p<0.005$). Consequently, when using the DoH indices for (closed-loop) feedback during general anesthesia, it is important to know that certain bolus doses of ketamine may render the DoH indices temporarily unreliable.

Observed SR values were relatively small. Median values of the maximum BSR for each case were zero for all the devices in the G 0.5, and below 0.8 % for in G 0.25 and control. Unfortunately, BSR values were observed too infrequently over the evaluated time window to take an unequivocal stand towards decreases BSR in the presence of ketamine.

4.2 Monitor Comparison

The monitor comparison within each dosage group at minute 1, 5, 10, and 15 resulted in no significant differences between the devices in the presence of ketamine. Ultimately, all three monitors are developed to prevent intraoperative awareness during anesthesia and are therefore designed with high sensitivity for high frequencies. The power increase in the β- (16–32 Hz) and γ-band (32–64 Hz) was detected by all monitors and consequently resulted in an increased DoH index. Although the calculations of each DoH are monitor-specific, their behavior in the presence of ketamine was similar. Thus, no tested monitor was superior in the presence of ketamine; meaning the anesthesiologist will detect an increased DoH output independently of the used monitor (BIS, Entropy, or NeuroSENSE).

Furthermore, the Bland-Altman analysis found that the RMSE decreased for increasing ketamine when comparing BIS to either SE or WAV. This suggests that the agreement of the two methods increased with the presence of Ketamine from a RMSE 9.74 to 2.85 for BIS vs. SE in G 0.5 and Control, and 4.87 to 0.29 85 for BIS vs. WAV in G 0.5 and Control. Without the knowledge of the exact algorithms calculating the DoH we can only

speculate on their reason and a test with a larger sample group is needed to confirm that this observation is reproducible and not a coincidence. The BSR thresholds are monitor-specific and may explain an increased agreement between the monitors in the absence of burst suppression.

4.3 Limitations

This study was designed as a comparative study using a novel case replay system. Besides the many benefits of our modified DAC replay system, replaying a digital signal sampled at 900 Hz means a loss of information compared to the original EEG signal obtained from a person's forehead. Furthermore, pre-recorded EEG is affected by the input filters applied during the original recording. A detailed filter characterization may be needed to fully reconstruct the raw EEG signal and more faithfully replay the EEG.

Next, the low amplitudes of EEG signals (µV) are highly prone to perturbation. However, shielding precautions were taken in form of a closed aluminium can around the replay system. The amplitude and frequency stability of our replay system needs improvement, in order to reduce the unexpectedly high ±8 WAV unit confidence interval in the Bland-Altman analysis of the case replay verification. A frequency-dependent amplitude enhancement could compensate amplitude decrease for very high and low frequencies. Another possible solution includes better shielding against interference. Finally, the use of other hardware options, such as a micro-controller DAC for replay might improve timing qualities.

Due to limited sample sizes (n=9), the observed, and expected, patient variability has pronounced impact on the group comparison. In contrast to other studies, evaluating the effect of ketamine on pEEG indices, we did not introduce ketamine after a stable DoH target value was reached. Consequently, we had no common DoH baseline measurement that can be used to objectively decrease the effect of interpatient variability or variability in the achieved DoH. This was determined by the study design of the previously conducted ketamine trial. In the future, our replay system could be used to replay EEG data from a ketamine trial with a prescribed DoH baseline to mitigate the impact of interpatient variability or variability in the achieved DoH.

Additionally, our findings only cover the effect of two ketamine dosages, [G 0.5, and G 0.25]. Clinical practice, however, includes a broader range of ketamine dose, which should be evaluated to improve our understanding of the effect of ketamine on pEEG. That said, the observed dose-dependent effect implies that a smaller ketamine dose might be more suitable for use of DoH guided anesthesia, and thus such further evaluations might not find clinically relevant results.

4.4 Conclusion

The presence of ketamine caused a dose-dependent increase in the DoH indices of three commonly used depth of monitors: BIS, Entropy, and NeuroSENSE. The reported increase in the anesthesia-atypical gamma band activity (32–64 Hz) may explain the behavior, resulting in DoH values slightly above the recommended range for general anesthesia when ketamine was present. Thus, for the anesthesiologist it is important to know that certain bolus doses of ketamine may render the DoH indices temporarily unreliable. However, and more encouraging, we did not detect a significant difference between BIS, Entropy and NeuroSENSE devices in their DoH behavior when ketamine was present.

Finally, replaying technology, once perfected, offers the potential to facilitate systematic evaluation of DoH monitors in the presence of adjunct drugs such as ketamine or dexmedetomidine, and contribute to establishing a more widely accepted standard for quantitative measures of anesthetic effect.

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