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Investigation of hysteresis during anesthetic-induced unconsciousness by using brain functional networks

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ABSTRACT

Hysteresis exists during the induction of and emergence from the anesthetic induced unconsciousness. Earlier researches considered this hysteresis as a pharmacokinetic delay, and its elimination has been the target of pharmacokinetics-pharmacodynamics (PK—PD) model for anesthetic agents. However, recent animal studies suggested that the observed hysteresis may be an intrinsic characteristic of the neural system. Thus, investigating the anesthetic-induced hysteresis in human subjects during the full course of general anesthesia was needed. In this work, we employed bispectral index (BIS) as the index for anesthetic effect-site concentration. The anesthetic effect was tracked by the graph theory-based measures obtained from the brain functional networks that was estimated from 60-channel EEG data. The hysteresis in this work is defined as the discrepancy between the estimated graph theory-based measures at the same BIS level during the process of anesthesia induction and emergence. Our results showed that the hysteresis quantified by graph theory-based measures exists in both delta and beta bands. Further, the frontal lobe and parietal lobe were identified to be responsible for the observed hysteresis. Moreover, it was observed that the proposed hysteresis index was significantly correlated with the time duration of the anesthesia induction and emergence. These findings suggested that the hysteresis might be an intrinsic characteristic of the human neural system, and it should be taken into consideration when designing PK—PD models for the anesthetics such as Propofol.

1. Introduction

Contrary to the traditional belief that induction of and emergence from general anesthesia (GA) are a mirrored process, it is commonly observed that the anesthetic effect-site concentrations at loss of consciousness is not sufficient to wake the patients during anesthesia [2,3]. That is, hysteresis exits in the dose-response curve of anesthetics. The observed hysteresis is traditionally considered as pharmacokinetic delay. To facilitate an easy control of the dosage of anesthetic agent during general anesthesia, the hysteresis is generally eliminated by optimizing the value of effect-site equilibration rate constant (ke0), so that a linear dose-response relationship could be obtained [1–3].

However, the assumption that the hysteresis is due to pharmacokinetic delay has been challenged by recent animal studies. Both mice and drosophila displayed hysteresis between the effect-site concentration of isoflurane and its behavior effect during induction of and emergence from GA [4,5]. Hence, it was suggested that such hysteresis cannot be solely explained by pharmacokinetic delay [5]. Further, the absence of adrenergic ligands in central nervous system (CNS) of mice was associated with the widened hysteresis loop, and four genes in the sleep system of drosophila were identified to be responsible for the change in hysteresis loop [4,5]. These evidences suggest that the hysteresis between effect-site concentration of anesthetic and its effect may be an intrinsic characteristic of the neural system. However, such hysteresis in human subjects is still a subject of debate and needs further investigation.

Studying hysteresis effect of anesthetics in human subjects requires properly defined surrogate measures for anesthetic effect and the effect-site concentration, respectively. Since the anesthetic expresses its effect at CNS, its effect-site concentration cannot be directly measured [6–8]. The bispectral index (BIS) has been shown to be linearly correlated with the effect-site concentration of Propofol in human subjects [9–11]. Thus, the BIS measured during anesthesia could be employed as a surrogate measure for the effect-site concentration of Propofol [12,13].

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Existing studies on hysteresis in human subjects only considered the difference in anesthetic concentration at loss of responsiveness to external stimuli during the induction and recovery from general anesthesia [14–16]. However, the voluntary response quickly diminishes once the anesthetics were administrated in bolus. It is therefore not possible to study the hysteresis after subject enters into the unconscious states. Fortunately, recent studies showed that the anesthetic agent affects the connectivity patterns of brain functional networks even after loss of response [17–19]. Thus, we employ the brain functional network and the graph theory-based measure as a surrogate to represent the anesthetic effect [20–24].

With BIS and graph theory-based measures employed as the surrogate for the anesthetic effect-site concentration and the anesthetic effect respectively, we then define hysteresis as the discrepancy between graph theory-based measures at the same BIS level obtained during the induction of and emergence from GA. To quantitatively study the observed hysteresis effect, a hysteresis index is calculated by integrating the obtained graph theory-based measures over the hysteresis loop. Further, we investigated the relationship between the proposed hysteresis index and the time duration of anesthesia induction and emergence.

2. Material and methods

2.1. Subjects

The study was approved by the ethics committee of the first affiliated hospital of Xi'an Jiaotong University, Xi'an, China. Experiments were carried out in accordance to the Declaration of Helsinki. Total 19 male subjects (32.9 ± 6.1 years of age) participated in this study. All subjects were fully informed and the written consent form was obtained before the experiment. All the subjects are drug-free, allergy-friendly to Propofol, and have no history of neurological or psychiatric conditions. Each participant fasted for over 8 h and had no premedication before the experiment.

2.2. Anesthesia protocol

Two experienced anesthesiologists conducted the experiments. Standard intraoperative monitors (Philips MP50, Boeblingen, Germany) and BIS monitor (Covidien, Mansfield, MA, USA) were used to monitor the vital signs and anesthesia depth, respectively. Adequate oxygen was delivered by a face mask. Subjects were instructed to keep their eyes closed throughout the experiment.

We considered the BIS value in the range of 40 ± 5 as the end-point of the experiment. The induction time of each subject was defined as the time duration from anesthetic injection to the first-time when BIS value declined into the range of 40 ± 5. Once the end-point was achieved, the BIS value was kept stable for at least 2 min. Then, the reverse protocol was initiated by setting the plasma concentration of Propofol to 0 μg/ml. During the emergence of anesthesia, subjects were given the verbal commands "open your eyes". The time duration from the stopping of drug infusion until the subject responds to the verbal command the first time was used as emergence time. After the completion of experiment, subjects were pushed into an anesthesia recovery room to wait for full recovery.

Propofol (Fresenius Kabi, Graz, Austria) is solely employed in the experiment to induce anethesia. The infusion of Propofol was performed by a TCI pump with in-built Marsh model operated at plasma concentration mode [25] (Injectomat TIVA Agilia, Fresenius Kabi Gmbh, Graz, Austria). Infusion started by setting the initial target plasma concentration of Propofol to 3.0 μg/ml. Then, the BIS value was closely monitored. Whenever the predicted plasma concentration reached the pre-set target concentration, with BIS value above the range of 40 ± 5, we increased the target plasma concentration at a step-size of 0.2 μg/ml until the BIS value reached the pre-defined end-point.

2.3. Electroencephalographic data acquisition and pre-processing

During course of anesthesia, 60-channels EEG data was recorded using a Synamps 2/RT system (NeuroScan, Singen, Germany). The EEG data was sampled at 1 kHz. All the channels were referenced to the left and right mastoids. Electrode impedance was kept below 5 kΩ throughout the experiment.

A block diagram of EEG signal processing and analysis pipeline was shown in Fig. 1. The EEG data was band-pass filtered into the range of 0.5–45 Hz. The recorded EEG data was segmented into 4-second epochs without overlap. Epochs containing excessive eye movement or any value higher than 3 standard deviations above the mean were manually removed. Then, the artifact-free EEG signals were re-referenced using a common average reference. Surface spatial Laplacian was applied to increase the topographical specificity and reduce the effect of volume-conduction [26,27].

Studies have shown that there are noticeable anesthetic-induced changes of EEG pattern on delta [28–30] and alpha [31–33] rhythms. The increased power of low-frequency oscillations and the anteriorization of alpha rhythm are proposed as EEG signatures of Propofol-induced unconsciousness [33]. Moreover, previous study showed that the beta band played a key role in the observed hysteresis phenomenon during Sevoflurane induced anesthesia. Hence, the pre-processed EEG signal was band-pass filtered in the frequency bands of delta (0.5–4 Hz), alpha (8–13 Hz) and beta (13–25 Hz) bands for further study. For the sake of completeness, the theta band (4–8 Hz) was also included. Finally, the EEG epochs were grouped based on BIS values. The pre-processed and segmented EEG epochs were then used for constructing the brain functional network.

2.4. EEG network analysis

The brain functional network was constructed by employing pairwise correlation between a pair of EEG channels as connectivity measure [34]. The pairwise correlation between two channels is defined as

$$r_{ij} = \frac{cov(x_i, x_j)}{\sqrt{var(x_i)var(x_j)}} \quad (1)$$

where $var(\cdot)$ and $cov(\cdot)$ represent the estimation of variance and covariance respectively. x_i represents the EEG signal at i -th channel. Using Eq. (1), the weighted adjacent matrix for all subjects was obtained by calculating the pairwise correlation between all possible pair of EEG channels.

Threshold employed to prune the obtained brain network was selected by preserving a proportion of the strongest connections, so that the degree of the networks can be maintained across subjects. We calculated the graph theory-based measures at every threshold level ranging from 10% to 50% with a step size of 10%, and we found that statistically significant difference on the obtained graph theory-based measures exists over almost all the selected threshold level. Hence, we set the threshold to 50% for further analysis.

2.5. Network analysis

Graph theory-based measures were estimated based on the thresholded weighted adjacent matrix. The network has totally *60* nodes with each EEG channel being a node. The basic graph theory-