Measure of the electroencephalographic effects of sevoflurane using recurrence dynamics

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Received 3 February 2007; received in revised form 6 June 2007; accepted 12 July 2007

Abstract

This paper proposes a novel method to interpret the effect of anesthetic agents (sevoflurane) on the neural activity, by using recurrence quantification analysis of EEG data. First, we reduce the artefacts in the scalp EEG using a novel filter that combines wavelet transforms and empirical mode decomposition. Then, the determinism in the recurrence plot is calculated. It is found that the determinism increases gradually with increasing the concentration of sevoflurane. Finally, a pharmacokinetic and pharmacodynamic (PKPD) model is built to describe the relationship between the concentration of sevoflurane and the processed EEG measure (‘determinism’ of the recurrence plot). A test sample of nine patients shows the recurrence in EEG data may track the effect of the sevoflurane on the brain.

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PACS: 87.19.Nn; 87.19.La; 87.80.Vt

Keywords: EEG; Anesthesia; Sevoflurane; Recurrence quantification analysis; Artefact reduction; Pharmacokinetic and pharmacodynamic model

Since the 1980s, the electroencephalogram (EEG) has been used to estimate anesthetic drug effects [19,29]; aiming to quantitatively measure the drug depression of neural activity. The success or failure of an EEG monitoring system of anesthetic drug effects depends on whether we can condense the complex information of EEG into a single parameter; which also can be shown to have some plausible neurobiological interpretation. Early attempts used spectral methods of analysis, such as the spectral edge frequency, the median frequency [30], or the bispectral index (BIS) [6,19,26,27,29,30]. Some of the more recent methods based on information theory (spectral entropy) and non-linear time series analysis (approximate entropy) have been also developed [4,33].

Previous studies have shown that neuronal activity is non-linear [20], so non-linear signal processing to analyse the raw EEG recording may be useful [12,28,43]. Assuming that the EEG signal arises from a purely deterministic or stochastic process (white noise), Lyapunov exponents [14–16] and correlation dimension [11,21,39] could describe the complexity of EEG data. Since non-linear measures have been used successfully to identify sleep stages [2,7,12,32]; it would be logical to investigate whether non-linear EEG analyses can be used to track anesthetic drug effects on the EEG. The first published work to monitor anesthetic drug effect via non-linear EEG analysis was that of Watt and Hameroff [37]. This was followed by use of the correlation dimension or approximate entropy [3,4,40] to estimate anesthetic drug effect via EEG recordings. However, the practical application of these existing non-linear measures is seriously limited because these methods require long, stationary and noiseless EEG data [10]. To overcome the drawbacks above, a recurrence quantification analysis (RQA) – that was originally proposed by Webber and Zbilut [38] – is employed in this study. It is claimed that RQA can describe the degree of determinism present in a short and non-stationary signal with noise [23,41,42]. In this study, the aim of this paper was to explore whether there is any correlation between the ‘determinism’ in the recurrence plot of EEG data and sevoflurane concentration. To ensure accurate RQA estimation, we have developed a novel filter as well.

To remove or reduce artefacts in EEG recordings previous methods based on frequency band, modelling, and time-scale transform have been proposed. This paper proposes a novel filter that combines wavelet transforms and empirical mode decomposition to reduce artefacts in the EEG signal. The determinism in the recurrence plot is then calculated. A test sample of nine patients shows the recurrence in EEG data may track the effect of the sevoflurane on the brain.
artefact filter based on wavelet transform with empirical Bayesian estimation and empirical mode decomposition (EMD). First, a six-level discrete wavelet transform, using a Sym8 wavelet, is performed on an EEG data of 4 s epoch. The previous work has shown that the Sym8 better approximates the EEG waveform, so that the EEG wave will be kept, once the wavelet filter has been applied to filter the noise embedded in EEG recordings. The EEG data at the frequency bands of 25–50, 12–25, 6–12, 3–6, 1.5–3 and 0.5–1.5 Hz are obtained. The slow frequency band of 0–3 Hz is removed in this study, the artefact signals such as the electrical activity of the heart, muscles and eyes often lie at this frequency band (the standard filter is 3–70 Hz in fourth generation monitor, BIS VISTA™, reference [17] p. 458). The EEG data at the frequency band of 25–50 Hz often includes a large amount of EMG (Electromyography) artefacts, so it should be discarded [18]. The amplifier and electrodes in the EEG measure system will bring some ‘white’ noise to EEG data, to remove the white noise that is possibly distributed in all of frequency bands, a Bayesian estimation is used to set up different thresholds for different scales [1], then, the retained information, above thresholds is used to reconstruct a new EEG series via an inverse discrete wavelet transform. The criteria of the threshold depend on the Bayesian formalism and assumed prior distribution, the details can be found in [19]. To further remove EMG artefacts and other noises in retained EEG series, empirical mode decomposition [13] is applied to break down the EEG series. For a given EEG data $s(t)$, the EMD method can decompose the EEG signal as a linear combination of intrinsic mode functions (IMFs), $C_r (n = 1, 2, \ldots , N)$, $N$ is the number of IMFs:

$$s(t) = \sum_{i=1}^{N} C_i(t) + r_{N+1}(t), \quad (1)$$

where $r_{N+1}(t)$ is the residual of the EEG data that presents a trend. The decomposing process depends the oscillatory property of data itself; that means that the number of IMFs is determined by the sub-oscillatory data. After EMD decomposition, it is found that EMG artefacts concentrate on the first IMF (the highest frequency components) and trend information on the $r(t)$ (the lowest frequency components). In this work, the first IMFs and residual are discarded. Then, a new EEG time series $(u_i)$ can be generated by adding other IMFs.

To obtain a recurrence plot (RP) proposed by Eckmann et al. [9], the following $N \times N$ matrix is first calculated by

$$R_{i,j} = \Theta (\varepsilon - ||x_i - x_j||), \quad i, j = 1, \ldots , N. \quad (2)$$

where $N$ is the number of the state space vectors, $\varepsilon$ is a predefined cutoff distance, $||\cdot||$ is the norm (e.g. the Euclidean norm) and $\Theta(x)$ is a Heaviside function. The phase space vector $x_i$ can be reconstructed by using the Taken’s time delay method, $x_i = (u_{i\tau}, u_{i(\tau+1)}, \ldots , u_{i(\tau+m-1)})$, based on the filtered EEG signal $u_i$. In this study, the EEG data of 4 s (400 data points) is applied to construct the phase space; the EEG data at different states are collected for the embedding dimension and time delay determination with a global false nearest neighbour method and a mutual information function [5,24,34] $m = 12$ and $\tau = 5$ are the best to represent the dynamics of the EEG data such as RQA entropy; the cutoff distance $\varepsilon$, which defines a sphere centred at $x_j$, if $x_j$ falls within this sphere, i.e. the state is close to $x_j$, then $R_{ij} = 1$; otherwise $R_{ij} = 0$, is set as 1.5 (in units of the standard deviation).

Based on the binary values of $R_{ij}$ (also called recurrence plots) a quantitative analysis method is proposed, called RQA [38,24,36]. More details regarding RQA can be found in [36]. The RQA quantifies the small-scale structures of the recurrence plots including the number and duration of the recurrences of a dynamical system. In this study, determinism (DET) is addressed. The ratio of recurrence points on the diagonal structures to all recurrence points is called DET, which is a determinism (or predictability) measure of a dynamic system. As for a deterministic process, it has an RP with very few single dots but many long diagonal lines. DET is described by

$$\text{DET} = \frac{\sum_{i=1}^{N} I_P(i)}{\sum_{i,j} R_{ij}}, \quad (3)$$

where $P(i)$ is the frequency distribution of the lengths of the diagonal structures in the RP, $l_{\text{min}}$ is the threshold, which excludes the diagonal lines formed by the tangential motion of a phase space trajectory, in this paper it is fixed $l_{\text{min}} = 2$.

The correlation between anesthetic drug effect index and anesthetic drug concentration provides construct validity for anesthetic drug effect monitoring [8]. In this study, we use a standard pharmacokinetic/pharmacodynamic (PK/PD) model to describe the relationship between sevoflurane concentrations and the EEG response (measured by the DET of the RQA). This was done by modeling the movement of sevoflurane from the arterial blood (end tidal) using the first order rate constant, $K_{eo}$. The value of $K_{eo}$ (2.4 min) was estimated from the relationship between end tidal sevoflurane and the spectral entropy of the EEG [25]. Briefly, the effect site partial pressure is estimated by a first-order effect site model [25]

$$\frac{dC_{\text{eff}}}{dt} = K_{eo}(C_{et} - C_{\text{eff}}), \quad (4)$$

where $C_{et}$ is the end-tidal concentration of the drug, $C_{\text{eff}}$ is the sevoflurane concentration at the effect site, and $K_{eo}$ is the first order rate constant for efflux from the effect compartment. The $C_{\text{eff}}$ is estimated by iteratively running this above model with a series of $K_{eo}$ steps. For each iteration, a non-linear inhibitory sigmoid $E_{\text{max}}$ curve is fitted to the data by the following equation [25]

$$\text{Effect} = E_{\text{max}} - (E_{\text{max}} - E_{\text{min}}) \times \frac{C_{\text{eff}}^y}{EC50^y + C_{\text{eff}}^y}, \quad (5)$$

where Effect is the processed EEG measure, the $E_{\text{max}}$ and $E_{\text{min}}$ are the maximum and minimum Effect for each individual patient, $EC50$ is the sevoflurane concentration at which Effect is midway between this maximum and minimum. $y$ describes the slope of the concentration–response relationship. $K_{eo}$ is determined from the iteration yielding the greatest coefficient of determination ($R^2$) for measured and modelled EEG Effect for each patient [25]. A non-linear inhibitory sigmoid $E_{\text{max}}$ curve was fitted to the brain (effect-site) concentration–DET relation-
ship (WinNonMix, Pharsight Corporation, CA, USA). From the fitted curve, values of pharmacodynamic parameters describing this relationship were derived, including $\gamma$ and EC50.

The first 40 s and the last 40 s of the DET time-course for each subject was averaged in order that a simple statistical comparison in DET values could be made during the periods of lowest and highest end tidal sevoflurane levels, respectively. To determine the statistical significance of changes in DET, these values were compared using a paired $t$-test, with a $p$-value of 0.05 considered significant.

Test subjects included nine patients with ASA physical status I or II scheduled for elective gynaecological, general or orthopaedic surgery. Patient exclusion criteria were: preoperative use of medication acting on the CNS, excessive weight or a history of gastro-oesophageal reflux that would not permit gaseous induction with sevoflurane, a history of cardiac, pulmonary, hepatic or renal disease, and use of any premedication. All subjects were fasted for at least 6 h before anaesthesia and received no premedication. Local hospital ethical committee approval was obtained, along with written informed consent from all subjects. We used a composite electrode, that is composed of a self-adhering flexible band holding three electrodes measuring the EEG between the forehead and temple. The sampling rate was 100/s, and a band filter of 0–50 Hz. Inspired and expired sevoflurane concentrations were measured at the mouth and sampled at 100/s. The more details can be seen in [25]. The data were recorded on a laptop computer and stored for later off-line analysis using MatLab (version 7; MathWorks, Natick, MA) computational and data analysis software.

First, the original EEG recordings were pre-processed by the novel filter. To show the effect of the novel filter on the typical EEG recordings, examples of four original EEG fragments (with increasing sevoflurane concentrations) are shown in Fig. 1I–IV (a) The filtered EEG data is shown in Fig. 1I–IV (b). Fig. 1I (a) and (b) show the effect of the filter in removal of eye-movement artefact, in the awake state. Fig. 1II (a) and (b) show that the slow waves were also removed by the filter. At the III and IV, EEG data mainly include low frequency waves (5–12 Hz) during the anesthesia. These fragments basically include typical artefacts in the EEG recordings. The performance of the filter can be found by the direct observations.

An example of an EEG recording with the induction of anaesthesia, and inspired and expired sevoflurane concentration are plotted in Fig. 2. After noise filtering, the determinism of the EEG data was estimated on sequential 4 s windows of EEG data (50% overlap). The end-tidal sevoflurane (the lower bound of the trace) concentration increases gradually, the amplitude of EEG recording increases with increasing sevoflurane concentration. The change in DET with time is shown in Fig. 1C. As the sevoflurane concentration increases, the DET of filtered EEG data increases, until it reaches a plateau.

The mean DET time-course is shown in Fig. 3 (bottom). An increase in DET with increasing sevoflurane concentration occurred consistently across subjects, although there was considerable variability in absolute values between subjects. This is reflected in the large standard area limits (bottom graph, Fig. 3). The average DET values during the first 40 s of recording were significantly lower than those during the last 40 s ($p = 0.036$, paired $t$-test).

The results of the modelled relationship between sevoflurane concentration and DET of the filtered EEG for nine patients are shown in Table 1.

The effects of sevoflurane on EEG data have been described by Jameson and Sloam [17]. The neural activity is synchro-

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**Table 1**

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<th>Parameters (mean(95%CI)) describing the relationship between DET of EEG and sevoflurane concentration</th>
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<tr>
<td>DET$_{Max}$</td>
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Fig. 3. Changes in effect-site sevoflurane concentration (top) and DET (bottom). The grey lines in the top graph are the effect-site time courses for each individual and the black line the mean time course. The shaded area in the bottom graph represents the standard error limits. The stars in the bottom graph indicate the time of loss of consciousness for each subject.

References


Acknowledgement

The authors would like to acknowledge the support of National Natural Science Foundation of China (60575012).