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Simultaneously Extracted Transient and Steady-State Evoked Responses during General Anesthesia: Variability of Different Rates

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Abstract— Unintended intraoperative awareness occurs in one to two individuals out of every one thousand treated with general anesthesia. Patients that experience intraoperative awareness have significant post-operative psychological sequelae. The ability to detect intraoperative awareness is currently suboptimal because the mechanism employed by anesthetic drugs to impair consciousness remains poorly understood. Studies have suggested that evoked potentials (EP) may be used to monitor the depth of anesthesia. Both transient and steady state responses can be simultaneously extracted using the Continuous Loop Averaging Deconvolution (CLAD) method with specially designed CLAD sequences. 20 Hz and 30 Hz jittered CLAD sequences in addition to 5 Hz isochronic and 40 Hz jittered CLAD sequences were applied in baseline awake and general anesthesia conditions. A qualitative method to assess the extracted EPs was developed in this study, termed Randomized Split Set Average (RSSA). The results showed that EPs extracted during general anesthesia require a greater number of sweeps to obtain a signal-to-noise ratio comparable to that observed in EPs extracted during the awake state. Therefore, the development of a real time or quasi real time EP monitoring system for anesthesia provides an increased challenge. The RSSA employed in this study is a useful method for assessing the signal quality of EP responses.

I. Introduction

Unintended intraoperative awareness, a period of consciousness occurring during surgery that is explicitly recalled by the patient after anesthesia, occurs in one to two individuals out of every one thousand undergoing general anesthesia [1, 2]. The mechanism of action of anesthetic drugs remains poorly understood. According to Sebel *et al.* [1], traditional clinical monitoring modalities are not completely effective in preventing intraoperative awareness. The cause of intraoperative awareness is currently unknown and it may be a multifunctional problem. Ghoniem *et al.* [2] reported that patients who experience intraoperative awareness developed significant post-operative psychological sequelae. Current methodology for monitoring awareness, such as the bispectral analysis (BIS) monitor, is empirically-based and was recently found not to provide any benefits over conventional assessment measures [3]. There are two forms of auditory evoked responses: transient responses and steady state responses. Transient responses are formed when successive auditory stimuli are applied at a rate that permits the response of the first stimulus to finish before the next stimulus is applied. In contrast, steady state responses are formed when successive auditory stimuli are applied at a rate that results in the approximate linear superposition of successive discrete transient responses, thus, forming a periodic response. A steady state response is best described by its magnitude and phase values in the frequency domain, and the transient response is best described with respect to the amplitude and latency of its peaks. Previous studies have suggested the use of evoked potentials (EP) to monitor the depth of anesthesia [4, 5]. Currently, there are two approaches that use EPs in anesthesia monitoring: 1) the use of low stimulus rate to elicit auditory evoked potential transient responses [4] 2) the use of high rate (40 Hz) isochronic stimulation to elicit auditory steady state responses [5]. However, a limitation of these studies is the inability to simultaneously extract both transient and steady state responses from high rate auditory stimulus sequences. In this study we aim to explore new developed methods that combine the extraction of both steady state and transient responses. Since the previous study [6] showed that stimulation rate might influence the extracted recording, different rates are explored. The extraction is made possible by the Continuous Loop Averaging Deconvolution (CLAD) method [7].

CLAD is a mathematical method developed to deconvolve overlapping evoked potentials obtained at any mean stimulation rate [7]. Specially designed CLAD sequences permit the extraction of both transient and steady state evoked potentials [7, 8, 9]. In time domain, CLAD utilizes a system of linear simultaneous equations that can be solved by matrix inversion [7, 8]. The system of equations can be written as the convolution of the time domain transient response referred to as a(k) with a stimulation sequence referred to as h(k). This convolution process occurs in the sensory pathway when a stimulus is evoked. Other spontaneous activity (i.e. EEG, EMG) is added to this “noise free” convolved signal before it reaches the recording amplifiers. Thus, a sweep averaging process is necessary to reduce noise (and to improve SNR). After averaging enough sweeps (~1000, typically), an estimation of the convolved signal is obtained:

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$$\hat{v}(k) = a(k) * h(k) + n_i(k) \tag{1}$$

where $n_i(k)$ represents the residual physiological noise. This convolved signal is represented in the frequency domain as:

$$\hat{V}(f) = A(f) \cdot H(f) + N_i(f) \tag{2}$$

For well-designed jittered sequences the deconvolution can provide an estimation of the transient response:

$$\hat{a}(k) = FFT^{-1}\left(\frac{\hat{V}(f)}{H(f)}\right) = a(k) + FFT^{-1}\left(\frac{N_i(f)}{H(f)}\right) \tag{3}$$

The CLAD sequence of stimuli is chosen to form a solvable set of equations (nonzero H(f)). However, if the stimuli are applied at constant inter stimulus intervals (i.e. isochronic), then the set of equations cannot be solved because H(f) contains many zeros. The last term of equation (3) is a noise shaping factor. It indicates how the residual noise is affected by the deconvolution process. If H(f) magnitude is less than one, the noise component at the frequency (f) will be amplified. The CLAD method can be used to extract both transients and steady state responses from high stimulus rate auditory sequences [8, 9].

Recently, McNeer *et al.* [6] studied the influence of auditory stimulation rates on evoked potentials during general anesthesia. This study assessed the 5 Hz transient and 40 Hz transient and steady state responses. Their findings revealed a significant stimulation rate dependent effect on the anesthetic transient waveforms. The transient responses produced by the 5 Hz and 40 Hz stimulation rates during anesthesia revealed that the frequency of the cortical oscillations, normally observed to be 40 Hz in awake subjects, was reduced to lower frequencies (~ 20 Hz) during anesthesia. Thus, it seems that for applications in anesthesia, the 40 Hz stimulation rate may be too high to be relevant. Also, it was revealed that 40 Hz steady state responses are mostly generated by the brain stem structures during general anesthesia in contrast to the cortical structures in the awake state [6]. Because cortical oscillations from higher stimulation rates reduced to lower frequency, it was deemed necessary to explore the effects of lower stimulation rates. The aim of the current study is to investigate the transient and steady states responses elicited by the 20 Hz and 30 Hz jittered CLAD sequences in addition to the 5 Hz isochronic and 40 Hz jittered CLAD sequences. In this study the 40 Hz stimulation sequence has a lower jittered value compared with the jittered value used by McNeer *et al.* [6] in order to obtain a better estimate of the steady state response.

II. Method

A. Data Collection and Processing

This study was conducted with the approval of the institutional review boards at the University of Miami and the Human Subject Research office at the Jackson Memorial Hospital. The electroencephalogram (EEG) was recorded using the SmartEPCAM system (Intelligent Hearing Systems (IHS), Miami FL) from electrodes placed (10/20 system) on the right mastoid (neg.), forehead (gnd.), and Fz (pos.) location. The recordings were amplified (gain 100,000), bandpass filtered from 1 to 1500 Hz (6dB/oct roll-off), and digitized (16 bits, 200 µs sampling period). The stimulus sequences were presented sweeps (swp) of 4710.4 ms duration. EEG was recorded. Each set of sweeps is pre-processed by an artifact rejection level algorithm followed by digital analog filters. The artifact rejection level (aRL) eliminates sweeps with artifacts larger than ±93 µVolt; the linear-phase digital filters have a band-pass (13-1500 Hz).

B. Auditory Stimulus Design and Delivery

Rarefaction clicks were applied to the subject’s right ear using an insert earphone (ER-3A Ethmotic Research, Elk Grove Village, IL). Each applied stimulus had a sound level of 82 dB SPL peak, which was calibrated in a 2-cc acoustic coupler using the precision sound level meter Quest Model 1800. Fig.1. A. shows the auditory stimuli designed for the present study; it is a composition of four auditory stimulus regions with increasing rate. The 5 Hz region has three 5 Hz isochronic sweeps, each one, lasting 204.8 ms. The Jitter Factor (JF) is a measure of how much a jittered sequence differs from an isochronic sequence [7, 8, 9]. Isochronic sequences have JF equal to 1.0. In the 20 Hz region is made of four identical 6 stimuli sequences are delivered, each one lasting 307.2 ms (JF = 1.415). The 30 Hz region is made of four identical 9 stimuli sequences are delivered, each one lasting 307.2 ms (JF = 1.429) and the 40Hz region is made of four identical 12 stimuli sequences are delivered, each one lasting 307.2 ms (JF = 1.370). A silence (no stimulus) region of 409.6 ms. The distribution of the average stimulation rate for each sequence in Fig. 1. B is plotted in Fig. 1. C.

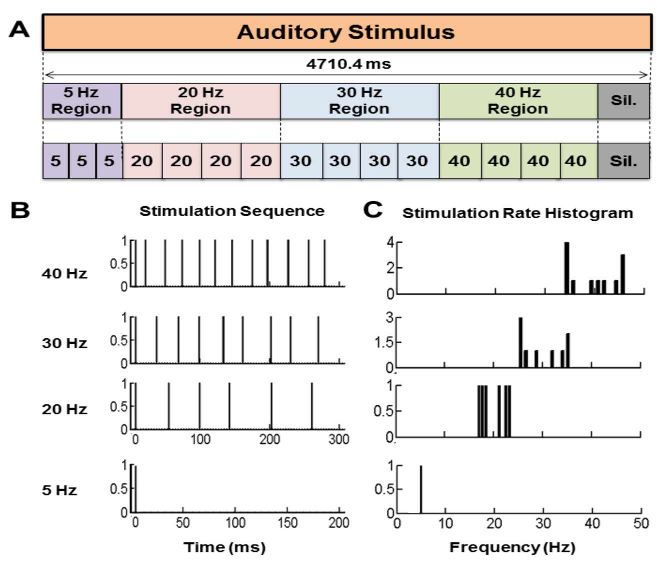

Fig. 1. A) The composite auditory stimulus is 4710.4 msec. long and is comprised of five regions (four stimuli and one silence). Each region is subdivided into individual sweeps as shown. B) Shows the temporal occurrences of clicks in each sweep for the four stimulation rates. C) Shows the histogram corresponding to each rate. There is little to no overlap between the distribution of stimulation rates for the 20, 30, and 40 Hz sequences. Isochronic sequences (5Hz) do not vary in stimulation rate.

C. Continuous Loop Averaging Deconvolution (CLAD)

For this study the CLAD sequences were designed to have sequences with noise attenuation characteristics (magnitude

H(f) greater than 1) for the frequencies within physiological interest (15Hz-900Hz). By using low-jittered CLAD sequences, the CLAD method elicits a convolved evoked response that approximates well the steady state response [8, 9].

The CLAD method, independently applied to the 20, 30, and 40 Hz regions, consists of the following steps:

1) The steady state response is extracted by performing an average of the full set measured EEG sweeps (typically 1000). The result is stored into the variable $\hat{v}(k)$, where $\hat{v}(k)$ is the steady state response.
2) The Fourier transform (FT) of the average of the full set is calculated and stored into the variable $\hat{V}(f)$.
3) The FT of the CLAD stimulation sequence is calculated and stored into the variable $H(f)$.
4) The result of step 2) divided step 3) is inverse FT producing the estimated transient response $\hat{a}(k)$, where $\hat{v}(k)$ is the transient response.

D. Randomized Split Set Average (RSSA): Evoked Potential Analysis Method

The RSSA method was developed to assess the quality of extracted EP. It displays many split set averages, referred to as subsets, obtained by randomizing the order of the original full sweep set. The range of variability of the RSSA is an indication of the amount of residual noise (mostly spontaneous EEG) and the variability of the evoked potentials. The RSSA method accounts for the nonstationary characteristics of the noise. If the residual noise and the generators of the EP responses remain stationary then the variability between the two subsets should be small.

The RSSA method consists of the following steps:

1) The average of the full set of sweeps (typically 1000) is performed and stored into the variable $<R_{01}>$, where $<R_{01}>$ is the average response value of the full set.
2) For **n** iteration (typically 100) the following procedure is performed:
   a) The order of the sweeps within the set is randomized by using a uniform probability distribution.
   b) The resulting random ordered set of sweeps is divided into two subsets that are independently averaged (i.e. $<R_0(n)>$, $<R_1(n)>$) and stored.
3) The average of the full set $<R_{01}>$ and the subset $<R_0(n)>$, $<R_1(n)>$ are compared to assess response quality.

E. Randomized Split Set Average (RSSA): Phasor Analysis

The RSSA method can be extended to incorporate phasor analysis. Phasor analysis is a frequency domain method that decomposes sinusoidal signals into the time-independent information of magnitude and phase at the fundamental frequency and its harmonics. To assess the quality of the averaged steady state response, phasor analysis is performed on each of the stored subset (i.e. $<R_0(n)>$, $<R_1(n)>$) and on the averaged full set (i.e. $<R_{01}>$) RSSA results.

Applying phasor analysis to the RSSA results consists of the following steps:

1) The FT of the average of the full set is calculated and stored into $R_{01}(f)$, where $R_{01}(f)$ is the frequency domain representation of the average of the full set.
2) For each **n** iteration, the FT of the averaged subset sweeps is calculated and stored into $R_0(n,f)$ and $R_1(n,f)$.
3) The magnitude and phase value at the fundamental frequency is calculated for $R_{01}(f_0)$, $R_0(n, f_0)$, and $R_1(n, f_0)$.
4) The phasor vector for $R_{01}(f0)$ and the subset $R_0(n, f0)$, $R_1(n, f0)$ are compared to assess response quality.

III. Results

The methodology developed in this study was tested in patients undergoing elective surgery. The result obtained from one awake subject (baseline, 818 swp, ± 83 μV aRL) is shown in Fig. 2. It shows the transient response for the isochronic 5 Hz sequence and the 20, 30, and 40 Hz low jittered sequences. For all figures, the dark line represents the average of the full sweep set; the gray area represents each subset average and the range of variability. The result obtained from one subject during maintenance stage of anesthesia (1.8% sevoflurane, 818 swp, ± 83 μV aRL) is shown in Fig. 3. Plotted is the transient response for the isochronic 5 Hz sequence and the 20, 30, and 40 Hz low jittered sequences. Compared to the awake subject, the anesthesia data showed a greater range of variability (gray area) for all conditions (stim. rate, transient or steady state EP type). The results obtained for Fig. 4 shows the phasor results of the awake (baseline subject, left column) and the anesthesia subject (right column) produced by the 20, 30, and 40 Hz low jittered sequences. In contrast to the awake condition, the steady state 40 Hz phasor vector direction and amplitude did not seem to vary much during general anesthesia, while the 20 and 30 Hz rate phasor vectors varied more. Additionally, the range of variability (gray area) for phasor vector was more spread for 20 Hz than 30 Hz.

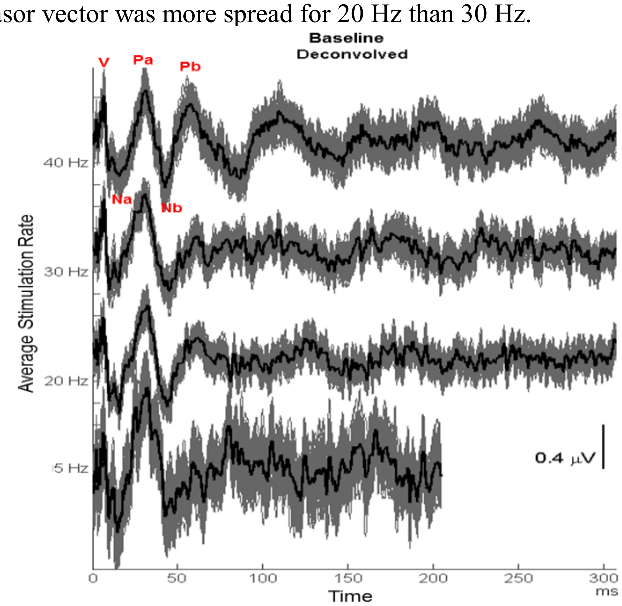

Fig. 2. The baseline transient response (no anesthesia, 818 sweeps, ±83 μV aRL) for the isochronic 5 Hz sequence and the 20, 30, and 40 Hz low jittered sequences. The dark line represents the average of the full sweep set; the gray lines represent each subset average of each randomized iteration determined by RSSA.

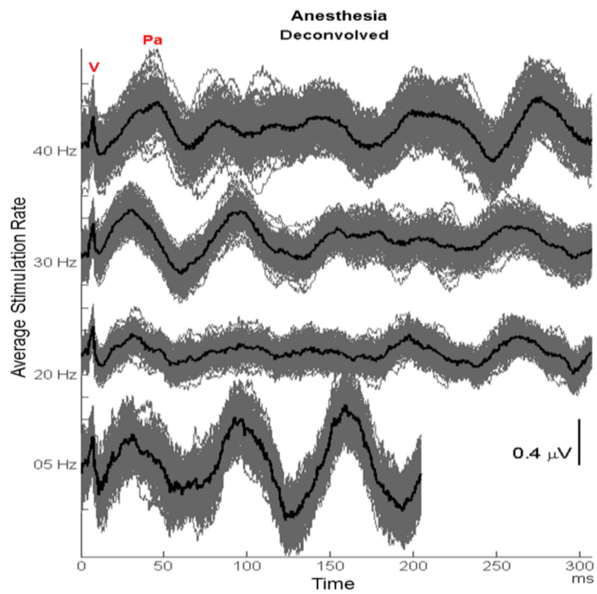

Fig. 3. The anesthesia transient response (1.8% sevoflurane, 818 sweeps, ±83 µV aRL) for the isochronic 5 Hz sequence and the 20, 30, and 40 Hz low jittered sequences. The dark line represents the average of the full sweep set; the gray lines represent each subset average of each randomized iteration determined by RSSA.

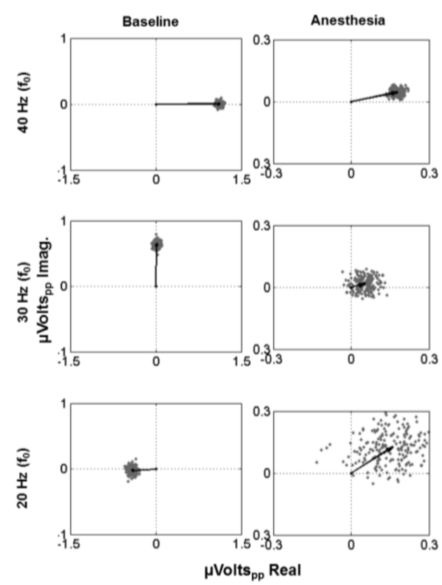

Fig. 4. Phasor plots of the fundamental frequency (f_0) of the 20, 30 and 40 Hz stimulus rates. (baseline left column, anesthesia right column). The dark line represents the vector of the averaged full sweep set; the gray points, each subset average of each randomized iteration determined by RSSA.

IV. Discussion and Conclusion

Deconvolved transient responses during anesthesia reveal important, low-frequency, cortical activity which is not reflected in the low amplitude steady state responses. This low-frequency activity is lost in the brain convolution process involved in the generation of the steady state responses. This observation makes the use of 40Hz ASSR less relevant as a facet for monitoring for intraoperative awareness. Preliminary results in this study seem to support the finding of McNeer et al [6] that during general anesthesia, oscillations normally observed in the awake state, are reduced to lower frequencies (~ 20 Hz), independent of stimulation rate. McNeer et al also reported evidence of a rate dependency of deconvolved EPs in the anesthetized state and evidence of significant differences of these responses. The RSSA method demonstrated that EPs obtained during anesthesia have a greater range of variability relative to those obtained during the awake state. This indicates that for anesthesia studies, a greater number of sweeps are required to obtain improved SNR performance. This finding increases the challenge of creating a real-time EP anesthesia monitoring system. Importantly, the RSSA methodology used in the current study provides a useful metric for assessing the quality of acquired EPs and can be implemented in future studies to measure variability in EP signals.

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