31st Annual International Conference of the IEEE EMBS
Minneapolis, Minnesota, USA, September 2-6, 2009

Long-term Assessment of Post-Cardiac-Arrest Neurological Outcomes with Somatosensory Evoked Potential in Rats

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Abstract—**Cardiac arrest (CA) can produce complex changes in somatosensory evoked potentials (SSEPs). Somatosensory evoked potentials (SSEPs) indicate the intactness of somatosensory pathways and are commonly used for brain function monitoring during surgeries. Multiresolution biorthogonal wavelet analysis was applied to SSEPs recorded during established CA experiments and post-CA long-term recovery periods in rats. Our results showed that during the first 4 hours after CA, the amplitudes of SSEP, defined here as the difference between the amplitudes of P23 and N20, decreased greatly while the inter-peak latencies between N20 and P23 increased greatly. In the long-term recovery period (within 72 hours), both the amplitudes of SSEPs and the interpeak latencies returned to the baseline. Our results suggest that the changes of SSEPs may represent the post-CA neurological injuries and recovery in the somatosensory afferent pathways. The results here lay ground work for establishing the relationship between SSEPs and post-CA neurological injuries and functional outcomes as well as deploying SSEP in clinical settings to monitor patients resuscitated from CA in the future.**

I. Introduction

Cardiac arrest (CA) is the leading cause of death in United States and in the world [1]. Neurological complications, such as coma and permanent vegetative states, have been recognized as the main cause of high post-CA mortality [2]. In order to develop effective treatments, it is necessary to first quantify the neurological outcomes from CA with some neurological markers. Animal experiments have shown that CA can produce complex changes in somatosensory evoked potentials (SSEPs) [3]. SSEPs can provide valuable information about the somatosensory afferent pathways all the way to the primary somatosensory cortex, including the dorsal columns of the spinal cord, the brain stem, the thalamus, and thalamus-cortical projections.

SSEPs usually have low amplitudes from less than one microvolt to several microvolts [4], resulting in relative low signal-to-noise ratios (SNRs). The most commonly applied method is ensemble averaging. This method has several drawbacks: firstly, it requires storage of large number of SSEPs for batch processing; also, it assumes that the variability of SSEP peak amplitudes and latencies does not carry valuable information about somatosensory afferent pathways [5]. Wavelet decomposition and reconstruction, on the other hand, can efficiently process nonstationary signals [6]; this method has been shown to be able to denoise biological signals while keeping the features of the signals intact [7].

The dominant peaks of SSEPs are named with a letter indicating polarity and a number showing the time delay relative to the onset of stimulation. N20, referred to the negative peak at 20 ms from the stimulation, is the primary cortical SSEP component following median nerve stimulation, and it is recorded over the parietal area contralateral to the stimulated median nerve. P23 is another component of SSEP and has polarity reversal to N20.

In order to characterize the changes of SSEPs before and after CA and study the relationship between post-CA neurological injuries and SSEPs, this paper used wavelet decomposition and reconstruction to denoise SSEPs recorded during global ischemic CA experiments in rats. Furthermore, denoised SSEPs were analyzed and main features were extracted including the amplitudes of N20 and P23 as well as the interpeak latencies throughout the experiments.

II. Procedure for Paper Submission

A. Globally Ischemic Rat Model of CA

6 male Wistar rats (350±25g) underwent 7-min ischemic CA experiments. This rodent model has been approved by Johns Hopkins School of Medicine and used to study neurological injuries from CA [8]. In brief, rats were mechanically ventilated with 1.0% halothane in N2/O2 (1:1). 15-minute SSEP baseline recording was followed by 5-minute washout to remove the residue effect of isoflurane on SSEPs. Ischemic CA was initiated by cessation of mechanical ventilation and block of airway and lasted for 7 minutes (Fig. 1). Cardiopulmonary resuscitation (CPR) was conducted with external chest compression lasting for 30 seconds to 1 minute until return of spontaneous circulation

Manuscript received April 23, 2009. This work was supported in part by National Institute of Health (NIH) Grants R01-HL071568 and R21-NS0544146.

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(ROSC). Sedative agents were avoided after resuscitation to minimize confounding effects on SSEPs.

B. Data Recording and SSEP Stimulation

5 Epidural screw electrodes were surgically implanted in the rats' somatosensory cortex for SSEP signal monitoring one week prior to CA experiments. All electrodes had light contact with the dura matter without penetrating into brain structures. The implantation results were validated after sacrificing the rats following 72-hour post-CA monitoring. SSEP signals were recorded through Tucker Davis Technologies (TDT) Neurophysiology Hardware and software (Alachua, FL). During the CA experiments, two pairs of 1cm stainless steel stimulating needle electrodes were placed in proximity to the median nerve in the right and left forelimbs for SSEP stimulation. Stimuli with pulse duration of 200 μs and frequency of 1 Hz were generated via the TDT Microstimulator Based Station. SSEP signals were continuously recorded from 15 minutes before CA as baseline to 4 hours post CA with sampling rate of 6103.5 Hz. 30-minute SSEP signals from the start of CA were excluded from further signal processing due to the mechanical noise induced by CPR.

C. Introduction of Wavelet Decomposition and Reconstruction

Traditional SSEP signal processing using Fourier Transform only provides the frequency domain information yet without time domain information. Multiresolution wavelet analysis can overcome the disadvantages mentioned above and has both temporal and frequency resolution. In the time domain, SSEP signals were analyzed with Multiresolution wavelets at both coarse and successively greater levels of temporal details. In the frequency domain, SSEP signals can be decomposed into independent spectral bands, especially clinical EEG subbands such as alpha (8-12 Hz), beta (12-35 Hz) et. There are two kinds of wavelet transforms including the continuous wavelet transform (CWT) and the discrete wavelet transform (DWT). CWT can be expressed as:

$$r(s,\tau)=\int f(t)\psi^{*}_{s,\tau}(t)dt \quad (1)$$

Where * denotes complex conjugation, $\psi^{*}_{s,\tau}(t)$ are the wavelet basis generated from scaling and translation of a single basic scaling function $\psi(t)$ (Eq.(2))

$$\psi_{s,\tau}(t)=\frac{1}{\sqrt{s}}\psi\left(\frac{t-\tau}{s}\right) \quad (2)$$

Where s is the scale factor, τ is the translation factor. Here the factor $\frac{1}{\sqrt{s}}$ is for energy normalization across different scales. CWT would produce redundant and nororthogonal wavelet coefficients due to continuous shifting of the basic scaling function. By sampling discrete scale factors and translation factors, DTW can produce orthogonal wavelet coefficients. Eq. (2) is modified into Eq. (3) as follows:

$$\psi_{j,k}(t)=\frac{1}{\sqrt{s_0^j}}\psi\left(\frac{t-k\tau_0 s_0^j}{s_0^j}\right) \quad (3)$$

Where j and k are integers, s_0 >1 is the fixed dilation step, and the translation factor depends on the dilation step.

D. Wavelet Denoising of SSEP

Quadratic biorthogonal B-splines wavelets [9] were chosen as the mother wavelets because their shapes are similar to the shape of SSEPs and they have optimal time-frequency resolution, and 5-level biorthogonal wavelet decomposition was conducted to the SSEPs recorded in CA experiments, generating 6 sets of wavelet coefficients a5 and d1-d5. A5 keeps the basic shape of SSEP peaks while the d1-d5 record different levels of detailed information of SSEPs. Our data suggests that the d1-d4 mainly contains the information of noise in SSEPs. Therefore, the wavelet coefficients d1-d4 were set to zero and SSEPs were reconstructed with wavelet coefficients a5 and d5.

E. Peak Detection of SSEP

Both the zero-crossing and local maximum/minimum detection methods were used to detect N20 and P23 in SSEPs accurately. Each SSEP sweep $S_i=\{s_1,s_2,s_3...s_N\}$ was first differentiated to generate another time series $X_i=\{x_1,x_2,x_3...x_{N-1}\}$ where

$$x_i=s_{i+1}-s_i \quad (4)$$

All the zero-crossing points were detected and further checked for local maximum/minimum. Our experimental data suggested that N20 was local minimum and P23 local maximum during the first 300ms after the onset of stimulation. The amplitudes of SSEPs were defined as the absolute difference between the amplitude of P23 and N20; the interpeak latency was defined as the absolute difference between the latency of P23 and N20 relative to the onset of the stimulation. The amplitudes and inter-peak latencies were calculated for all SSEPs. SSEPs (Mean±SD) from each rat were finally normalized based on their individual baseline values for further comparison.

III. RESULTS AND DISCUSSION

Figs. 2 and 3 show an example of the changes in SSEP amplitudes and inter-peak latencies throughout a CA experiment and the following post-CA 72 hours. Compared to the baseline, the SSEP amplitudes decreased and the interpeak latencies increased greatly. Similar changes were observed in all rats (Table I & Table II). SSEPs can reflect the integrity of somatosensory afferent pathways. Electrical stimulation was applied to the median nerve and the sensation signals travel along the median nerve from distal to

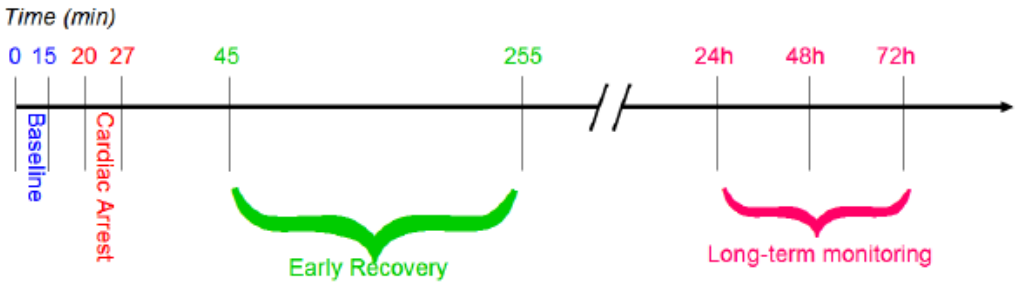

Fig. 1 The timeline for CA experiments in rats mainly including baseline, CA and post-CA first 4-hour early recovery as well as post-CA neurological deficit score evaluation at 24, 48, and 72 hours.

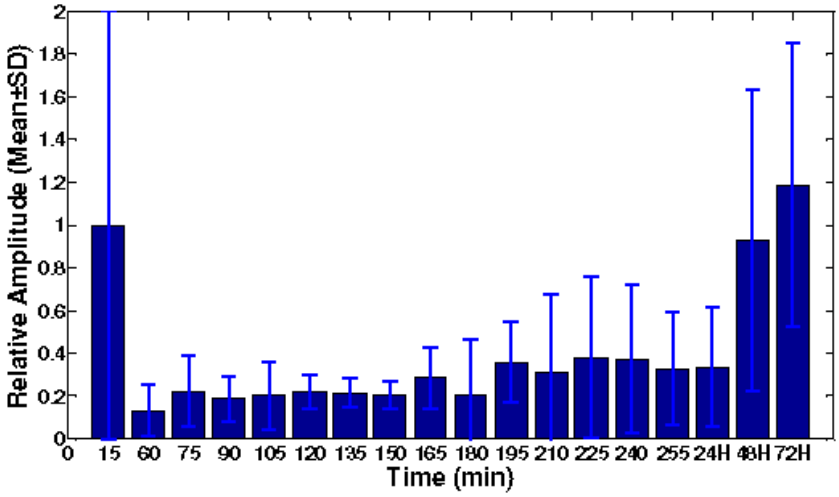

Fig. 2 Relative amplitude (Mean±SD) during different time slots throughout the CA experiments and the following 72 hours in a rat. Both the mean and standard deviation (SD) were normalized to the values in baseline. As shown in the figure, the amplitudes of SSEPs (the absolute different between amplitudes of P23 and N20) dropped significantly during the first 4 hours following CA compared to the baseline. It is also notable that the amplitudes of SSEPs slowly increased throughout the period. In the 48 and 72 hours after CA, the amplitudes of SSEPs greatly increased back towards to the baseline. The same trend could be observed in the relative SD of SSEPs.post-CA neurological deficit score evaluation at 24, 48, and 72 hours.

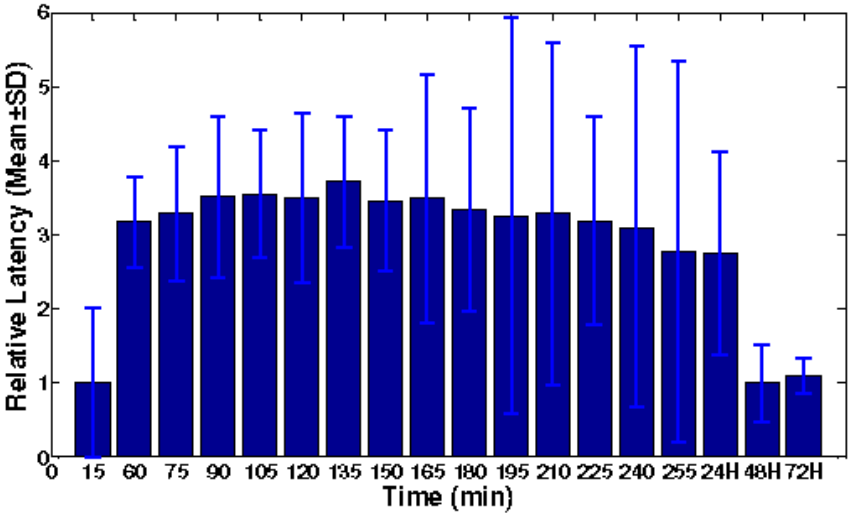

Fig. 3 Relative latency (Mean±SD) during different time slots throughout the CA experiments and the following 72 hours in a rat. Both the mean and standard deviation (SD) were normalized to the values in baseline. As shown in the figure, the inter-peak latencies between N20 and P23 increased significantly during the first 4 hours following CA compared to the baseline. In the 48 and 72 hours after CA, the inter-peak latency greatly decreased back towards to the baseline.

Table I Relative mean amplitudes in different periods in all rats

Time	15	60	75	90	105	120	135	150	165	180	195	210	225	240	255	24H	48H	72H
#1	1	0.09	0.24	0.36	0.47	0.55	0.62	0.70	0.74	0.72	0.67	0.71	0.69	0.67	0.62	1.00	1.13	-----
#2	1	0.001	0.18	0.24	0.28	0.40	0.50	0.52	0.52	0.50	0.44	0.54	0.52	0.55	0.58	0.48	-----	-----
#3	1	0.25	0.29	0.27	0.29	0.24	0.26	0.23	0.26	0.24	0.30	0.30	0.31	0.26	0.32	0.48	0.88	-----
#4	1	0.20	0.27	0.28	0.36	0.42	0.25	0.22	0.27	0.27	0.37	0.34	0.30	0.35	0.29	0.57	0.60	0.63
#5	1	0.13	0.22	0.19	0.20	0.22	0.22	0.20	0.28	0.20	0.36	0.31	0.38	0.37	0.33	0.33	0.93	1.19
#6	1	0.26	0.31	0.27	0.24	0.25	0.16	0.22	0.23	0.17	0.15	0.20	0.17	0.20	0.22	0.36	0.49	0.70

Table II Relative mean latencies in different periods in all rats

Time	15	60	75	90	105	120	135	150	165	180	195	210	225	240	255	24H	48H	72H
#1	1	0.09	0.24	0.36	0.47	0.55	0.62	0.70	0.74	0.72	0.67	0.71	0.69	0.67	0.62	1.00	1.13	-----
#2	1	0.001	0.18	0.24	0.28	0.40	0.50	0.52	0.52	0.50	0.44	0.54	0.52	0.55	0.58	0.48	-----	-----
#3	1	0.25	0.29	0.27	0.29	0.24	0.26	0.23	0.26	0.24	0.30	0.30	0.31	0.26	0.32	0.48	0.88	-----
#4	1	0.20	0.27	0.28	0.36	0.42	0.25	0.22	0.27	0.27	0.37	0.34	0.30	0.35	0.29	0.57	0.60	0.63
#5	1	0.13	0.22	0.19	0.20	0.22	0.22	0.20	0.28	0.20	0.36	0.31	0.38	0.37	0.33	0.33	0.93	1.19
#6	1	0.26	0.31	0.27	0.24	0.25	0.16	0.22	0.23	0.17	0.15	0.20	0.17	0.20	0.22	0.36	0.49	0.70

proximal; they further go into the dorsal part of the spinal cord and up to brainstem via both primary afferents and secondary afferents. The signals then ascend all the way to the thalamus and in the end activate the somatosensory cortex where SSEPs are recorded [10]. The decrease in SSEP amplitudes and increase in inter-peak latencies may indicate the neurological injuries in the somatosensory afferent pathways. In our experiments, the amplitudes and inter-peak latencies of SSEPs at 24, 48, and 72 hours go towards the baseline levels; this may represent the gradual neurological recoveries after CA. Further experiments will be carried out to correlate post-CA functional outcomes with SSEP amplitudes and inter-peak latencies to establish their relationship; meanwhile, post-CA histological experiments will be performed to identify the neurological injuries in the somatosensory pathways.

IV. Conclusion

Multiresolution wavelet analysis was conducted to SSEPs recorded during ischemic CA experiments in rats and the following 72 hours after CA. Our results showed that the amplitudes of SSEPs decreased during the first 4 hours after CA and gradually returned to the baseline within 72 hours, and the inter-peak latencies of SSEPs increased significantly during the first 4 hours after CA and decreased back to the baseline within 72 hours. The changes in SSEPs may represent the neurological injuries in the somatosensory pathways and long-term post-CA neurological recovery, though future in depth research is needed. SSEP is commonly adopted for clinical neuro-monitoring; our animal model experiments and SSEP signal analysis here laid the groundwork for deploying SSEP in clinical settings to monitor patients resuscitated from CA in the future.

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