Discovery of Long-Latency Somatosensory Evoked Potentials as a Marker of Cardiac Arrest Induced Brain Injury

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Abstract— **The use of Somatosensory Evoked Potentials (SSEPs) has been an established electrophysiological tool for diagnosis of neurological disorders or injury. We use SSEP for the prognostication of outcomes after hypoxic-ischemic brain injury. Previous studies on rats with median nerve stimulation have primarily focused on short-latency SSEP within 30msec after stimulus. This study shows that long-latency SSEP (LL-SSEP) within 30-100msec is also of unique importance in monitoring brain injury induced by cardiac arrest (CA) and prediction of long-term recovery. In this study, 16 rats underwent either a 7min or 9min hypoxic CA. The Neurological Deficit Score (NDS) measured at 72hr post-CA was used to specify good outcome (NDS≥50) and poor outcome (NDS<50). Firstly, the LL-SSEP showed sharp responses to CA insults—change in P60 peak in the time-frequency space, Shannon entropy in the time domain, and wavelet entropy in the frequency domain. Secondly, LL-SSEP during early recovery had significant prognostic value: the Shannon entropy within 60min post-CA was higher for the good-outcome group (*p*-value=0.02, Student's t-test) and a delayed P60 exclusively predicted poor outcome. Thirdly, the LL-SSEP was significantly different than the short latency response. Since the LL-SSEP occurs well beyond the time delays for production by the thalamocortical network, it may be an independent cortical response, and may reflect the recovery of cortical neurons. The discovery of LL-SSEP should have significant clinical potential in assessing the recovery of the cortical function after brain injury and should be helpful in understanding the mechanism of thalamocortical arousal.**

Keywords— **somatosensory evoked potential, long-latency, cardiac arrest, neural monitoring, prognosis, entropy.**

I. Introduction

Somatosensory evoked potentials (SSEPs) consist of a series of waves that reflect sequential activation of neural structures along the somatosensory pathway. Abnormalities in SSEPs indicate dysfunctions at certain levels of the pathway. SSEPs are conventionally used for the evaluation of hypoxic-ischemic brain injury from cardiac arrest (CA), where neurological complications have been a leading cause for morbidity and disability after CA[1]. Bilateral loss of cortical N20 is a strong indicator of cortex injury by CA [2], and post-CA SSEP helps to predict long-term outcome with a very high specificity, but moderate sensitivity [3].

In humans, median nerve evoked short-latency (SL) SSEP components (N13, N20, P25[4]) that reflect thalamocortical responses and long-latency (LL) components (N35, P45, N70, P95 [4]) that reflect corticocortical responses [5, 6] have been studied. Prior research has looked into LL-SSEP in humans (N70) as a secondary indictor to the N20 to improve prognosis. Absence or a delay ≥120ms of N70 with N20 present strongly correlates with adverse outcomes [3, 4]. However, animal studies of LL-SSEP are rare to the best of our knowledge, leaving a gap in the translational research of hypoxic-ischemic brain injury.

In this study, we investigate dynamics of LL-SSEP during CA and early recovery using information theoretic measures and time-frequency analysis. The prognostic value of LL-SSEP is examined using the entropy measure. We also compare the evolution of LL-SSEP with that of the SL-SSEP, and discuss the physiological foundations for the difference. The primary goal of this study is to understand the role of LL-SSEP and its representation of cortical functions. In this way, we hope to gain more insight into to loss and return of SSEPs due to hypoxic-ischemic insults, and how the recovery process associate with neurological outcomes.

II. Experiment

The experiment was done on a rat model [7, 8] of cardiac arrest. The protocol was approved by the Institutional Animal Care and Use Committee at the Johns Hopkins University School of Medicine. 16 adult male Wistar rats underwent a 7min (n=8) or a 9min (n=8) hypoxic-ischemic cardiac arrest. Five epidural screw electrodes (Plastics One, Roanoke, VA) were implanted in the somatosensory cortex in both left and right cerebral hemispheres, with a ground in the parasagittal right frontal lobe. The rats were allowed to recover for one week before the experiment.

At the beginning of the experiment, the rats were anesthetized and intubated for mechanically ventilation with 1.5% isoflurane in 1:1 N_2/O_2. A 15-min baseline SSEP was recorded from bipolar cortical electrodes, followed by 5-min washout to remove the residual effect of isoflurane. At the end of washout, CA was initiated by clamping the endotracheal tube to stop mechanical ventilation. The total

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duration of asphyxia was calculated from the point when the mean arterial pressure (MAP) fell below 10mmHg, and lasted for 7 or 9 min. Cardiopulmonary resuscitation (CPR) was performed with external chest compressions and mechanical ventilation until return of spontaneous circulation (ROSC), indicated by a rise in MAP over 60mmHg.

Bipolar SSEP signals were recorded with Tucker Davis Technologies (TDT) Neurophysiology Hardware and software (Alachua, FL). The median nerves were stimulated using two pairs of needle electrodes placed in the right and left distal forelimbs. A 0.6mA stimulation pulse with duration of 200μs was given alternatively to the left and right forelimbs at a unilateral stimulation frequency of 0.5Hz. The first 150ms of SSEPs were recorded at a sampling rate of 6103.5Hz. Signals were continuously recorded for 1 hour after the onset of CA. For the next 3 hours, SSEPs were recorded in 15min intervals. Functional evaluation was performed using the Neurological Deficit Score (NDS) which ranges from 0-80 at 24hr, 48hr and 72hr post-CA.

III. Methods

A. Time-Frequency Analysis

Time-frequency (TF) representation on SSEP signals has served an important indicator of hypoxic-ischemic injury and spinal cord injury [9, 10]. Short Time Fourier Transform (STFT) is a commonly used technique, which is essentially a short-term fast Fourier transform within moving windows to track the temporal-spectral dynamics. In discrete-time STFT, a time series $x(n)$ is split into overlapping windows to reduce artifacts at the boundary. Mathematically, this is expressed as:

$$STFT\{x(n)\} \equiv X^w(t,f) = \sum_{n=-\infty}^{\infty} x(n)w(n-t)e^{-j2\pi fn} \qquad (1)$$

where $w(n)$ is a window function. For this study, a hamming window was chosen. At a sampling rate of 6103.5 Hz, the window size is set to be 30 data points, which corresponds 5ms, and the overlap is set to be 20 data points.

The magnitude square of the STFT yields the TF spectrogram of the signal:

$$spectrum\{x(n)\} \equiv [X^w(t,f)]^2 \qquad (2)$$

B. Entropy Analysis

Entropy from information theory viewpoint is a measure of the uncertainty of a random variable. We used two typical entropy measures: One is the classical Shannon entropy [11] as a measure of the entropy of amplitude distribution in time domain. The other is wavelet entropy to assess the entropy of energy distribution over frequency subspace. The wavelet approach is especially suitable for analysis of short duration neural signals [12] such as SSEP.

a) Shannon Entropy (SE)

The Maximum Likelihood estimator (MLE) of SE with Miller-Madow bias correction[13] is defined as

$$\hat{SE}_{MM} = -\sum_{i=1}^{M} p_i \log_2 p_i + \frac{\hat{m}-1}{2N} \qquad (3)$$

where p_i is probability of finding the signal in the i^{th} bin while the full range of the signal is equally divided to M interconnected and non-overlapping bins, and $\hat{m}$ is the number of bins with non-zero probability. We will use $\hat{SE}_{MM}$ to compensate the negative bias by MLE alone.

b) Wavelet Entropy (WE)

To measure spread of the spectrum of a signal distributed in different frequency subbands, we use multidimensional Discrete Wavelet Transform (DWT) for wavelet decomposition of SSEP. We choose as the basis function the Daubechies 5 function, because of its similarity to SSEP signals in shape. Then, the wavelet expansion of signal $x(i)$ is

$$x(i) = \sum_j \sum_k C_j(k)\psi_{j,k}(i) \qquad (4)$$

where $\psi_{j,k}(i)$ is scaled and translated basis function from the mother wavelet and with parameter j and k, and $C_j(k)$ is the wavelet coefficient on the j^{th} decomposition level. The energy distribution in each subband is used for estimating WE as follows as:

$$WE = -\sum_j \frac{E_j}{\sum E_j} \log_2 \frac{E_j}{\sum E_j} \qquad (5)$$

where $E_j = \sum_k |C_j(k)|^2$ is the energy in the j^{th} subband.

IV. Results

For all of the 16 experiment rats, besides the most prominent short-latency peaks N10 and P15, there was a peak around 60ms in the bipolar SSEPs, which by convention is termed as P60 in this study (see the inlet waveform in Fig. 1). This long-latency peak was different from short-latency peaks in that its amplitude was lower, and while its latency in each rat remained consistent with time, the latency was inconsistent across rats and varied within 50-70ms.

A. Evolution of SL- and LL-SSEPs after CA

In all experiments, the long-latency peaks recovered soon after CA, while short-latency peaks had low amplitudes until a mean interval of 60min after ROSC. In order to

quantify the change of short- and long-latency after CA, N10 and P60 peaks were detected for every 20-sweep average and their amplitudes were normalized with respect to baseline for comparison.

As shown in Fig. 1, both N10 and P60 amplitudes dropped instantly upon onset of asphyxia until they reached a minimum, but they exhibited distinct recovery patterns. The P60 amplitude rebounded close to the baseline within 30min post-CA, and grew to surprisingly large amplitude during early recovery. There were some oscillations in its evolution. In contrast, short-latency followed a gradually increasing trend and only reached 50% of the baseline value within the first hour of recovery.

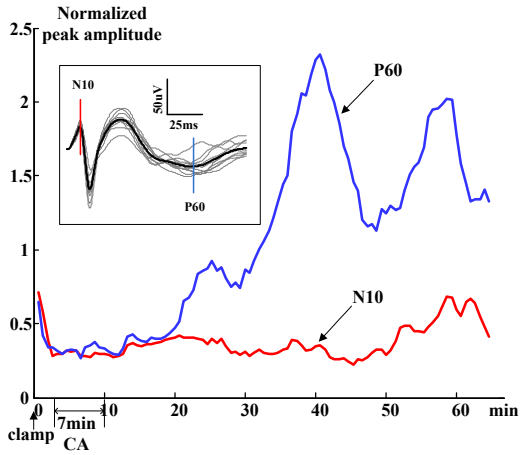

Fig. 1 The evolution of normalized N10 and P60 amplitude from the beginning of cardiac arrest (CA) up to 60min in a 7-min CA experiment. The inlet in the figure shows a typical SSEP waveform from baseline with N10 and P60 marked

B. *Monitoring of CA-Induced Brain Injury*

STFT was used to track the change of long-latency of SSEP in time-frequency domain. We took 2-min averages (60 sweeps) during the first 0-32 min of an experiment in which CA started from the 5th minute. For the implementation of STFT, we applied a 5ms long moving window with two-third overlapping, and computed FFT in each window to obtain the TF spectrogram. As we can see from Fig. 2, there is a concentrated peak in TF spectrum prior to CA that becomes widely dispersed during CA and gradually returns to the baseline pattern at about 10min after ROSC. This degree of dispersion can be a visible indicator of hypoxic-ischemic brain injury.

The TF spectrum enables us to visualize the change of LL-SSEPs in temporal-spectral manner. To quantify this change, we used SE for measuring changes in time-domain and WE for measuring changes in frequency-domain. For the same recording as Fig. 1, SE and WE were computed on each raw sweep, and were normalized to [0, 1] with respect to the full spans. As shown in Fig. 3, SE decreased dramatically at the onset of CA and remained low until 10min post-CA. In contrast, WE increased during CA and decreased towards baseline during recovery.

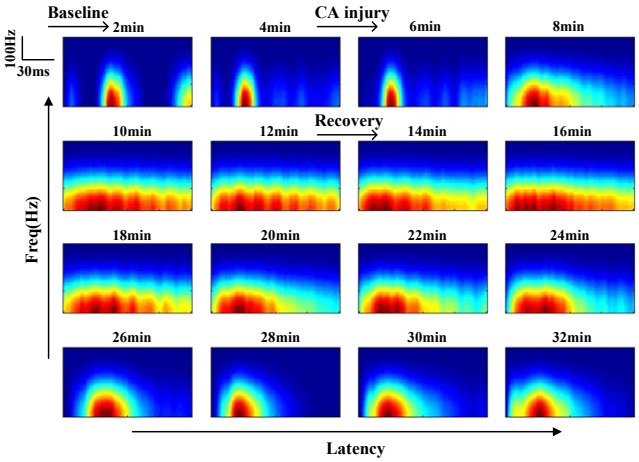

Fig. 2 Time-frequency spectrogram of long-latency SSEP during the first 0-32 min in a 7-min CA experiment. The time of onset of CA in this case is the 5min mark. Each subplot is the STFT spectrogram of a 2-min averaged SSEP waveform ranging from 30 to 150 ms

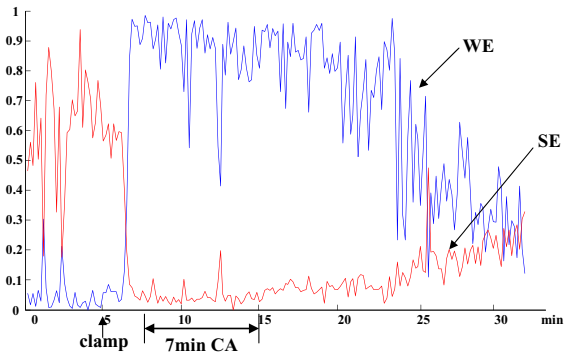

Fig. 3 The time evolutions of Shannon entropy (SE) and wavelet entropy (WE) of long-latency SSEP during the first 0-32 min in a 7-min CA experiment. The entropies are expressed in arbitrary unit

C. *Prediction of Neurological Outcomes*

The LL-SSEP is not only indicative of ischemic brain injury but is also predictive of long-term recovery. The SE turned out to be a promising measurement of long-latency for prognosis. We compared the averaged SE based on functional outcomes. The classification of rats into good and poor outcomes was based on NDS evaluated at 72hr post-CA with a cutoff at NDS=50. The *p*-value of a two-tailed t-test with unequal variance assumption was used to evaluate the statistical difference between the two groups.

The results showed that very early during recovery, SE was significantly larger for good-outcome group (p-value = 0.022 at 60min post-CA). This difference became insignificant once SE recovered to near baseline values.

We also examined P60 amplitude and latency as predictors. Result showed that a delayed P60 within 90min after ROSC predicted poor outcome with 0% false positive rate, while early arrival of P60 had no predictive value; the peak amplitude of P60 was unrelated with neurological outcome.

V. Discussion

We evaluated the value of LL-SSEP in monitoring CA-induced brain injury and predicting outcomes. We illustrated that the STFT pattern of long-latency became dispersed during CA and recovered to near baseline pattern around 10min after ROSC. In agreement with the change of STFT, the Shannon entropy of long-latency dropped during CA and gradually returned around the same time. The wavelet entropy followed an opposite trend due to the reduction of low-frequency components during CA. The superiority of using long-latency as a marker over short-latency lies in the benefit of using SE and WE on each raw sweep, without needing hundreds of sweeps for signal averaging.

The LL-SSEP played a unique role in our data for predicting outcomes well ahead of other electrophysiological makers such as EEG and SL-SSEP. The prognostic value of P60 latency is very similar to that of N70 in humans [4, 6], which predicts poor outcomes by absence or delayed latency with 100% specificity, but fails to predict good outcomes.

The different recovery patterns of LL and SL-SSEPs points towards different neural origins. The quicker recovery of LL-SSEP suggests lower vulnerability of the cortical function, given the hypothesis that SL-SSEP reflects thalamocortical activity and LL-SSEP reflects corticocortical interaction. More interestingly, in 7 of 16 rats, P60 amplitudes in early recovery became greater than the baseline. We speculate that this may be due to strong oscillations among cortical neurons that play a role in the arousal of the brain. To justify the origins of short- and long-latencies, we will need further experiments with thalamocortical recordings.

VI. Conclusion

We present an investigation of LL-SSEP in hypoxic-ischemic CA and post-CA recovery in a rat model. We define LL-SSEP as the evoked potential after 30ms and characterized it by P60. Our results show that the LL-SSEP showed remarkable changes after CA in both time- and frequency-domains. Entropy of LL-SSEP was capable of predicting good or poor outcome very early during recovery. A delayed P60 was a reliable sign for poor outcome. The recovery pattern of LL-SSEP differentiates its origin from that of SL-SSEP. We propose that the origin of LL-SSEP is cortical, and thus the loss and return of LL-SSEP reflect injury and recovery of the cortical activity; however, this remains yet to be fully elucidated.

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