35th Annual International Conference of the IEEE EMBS
Osaka, Japan, 3 - 7 July, 2013

Linear Model of Peripheral Nerve after Surgical Manipulation: Preliminary Report in Animal Study and Model Shift

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Abstract— **Generally, the neurophysiologic intra-operative monitoring (NIOM) is acknowledged to correlate with reducing the risk of perioperative neurological deficits. This electrophysiological method is commonly used and neurosurgeons could aware where the nervous system is at risk of being permanently injured while doing the operation under NIOM. However, this monitoring is quite a qualitative evaluation. Neurosurgeons have to use their own experiences to consider and made the estimation. Traditionally, the peripheral nerve function can be preserved by continuous electromyography (EMG) and compound muscle action potential response (CMAP) monitoring. The spike and burst EMG occur when the nerve trunk is irritated or damaged. Decreased amplitude of CMAP response is also considered as nerve damage even it might cause from a severe irritation. By using this information, the peripheral nerve function is qualitatively evaluated by the surgeons. This present study proposed a new predictive nerve model for peripheral nerve function prediction. This input and output data were used for nerve modeling in each condition. The results showed that parameters of the linear nerve model had significantly differences and tendency changes in each nerve condition. Therefore, the proposed method for predicting the nerve function by the shifted linearly nerve model might be a promising approach for peripheral nerve function estimation in the human nerve model.**

I. Introduction

Preservation of peripheral nerve functions during surgery is critically important. The peripheral nerve is possibly permanently damaged during the operation such as tumor dissection which resulted in peripheral nerve palsy to the patient.

Possible way to preserve peripheral nerve functions is the uses of continuous electromyography (EMG) monitoring [1-4]. During the operation, surgical manipulations including compressing, stretching, pulling and mechanical irritation to the nerve trunk can induce a spike and burst EMG signal. This EMG spike and burst can be converted to a sound for warning to the surgeon. The EMG bursts are considered as a reliable predictor for preserving nerve function. However, this method is quit sensitive and does not correlate with short- and long-term peripheral nerve function because amplitude and duration of EMG bursts reflect just the irritation levels to the peripheral nerve [1, 2].

Another approach for preserving peripheral nerve function is electrically evoked peripheral nerve response or compound muscle action potential response (CMAP) [5-9]. This CMAP response will be occurred after applying either constant current or voltage to the nerve. Decreasing in amplitude of CMAP response indicated a remaining nerve function post-operation [5-9]. 50% decreasing in amplitude is considered as a safety criterion to the peripheral nerve [6]. Nevertheless, decreasing in amplitude of CMAP response might be caused by nerve damaging or just severe irritation which can recover its function within a year. Presently, there is a commercialized product available on the market named neurophysiologic intraoperative monitoring (NIOM). Surgeon can monitor those signals for peripheral nerve function preservation. However, this preservation of peripheral nerve function is still qualitative evaluation by the surgeon. Completely removal of tumor without nerve damaging is ideal.

This study aims to investigate a feasibility of nerve damage prediction by considering CMAP responses. We first tried on the animal nerve (rat's sciatic nerve) instead of human nerve.

II. Materials and Methods

A. Signal acquisition and Electrical nerve stimulation

The experiment was conducted under animal ethic approval. This study included 4 sciatic nerves (n=4) of 2 male Wistar rats (age, 8 weeks; weight, 300 grams).

Figure 1 shows an overview of the signal acquisition and the electrical nerve stimulation systems. Four EMG signals were recorded through bipolar needle electrodes that placed on the Tibialis anterior, Gastrocnemius, Vastuslateralis and Semimembranosus muscles of the rat's leg. These EMG signals were amplified by 200 times and sampling at the rate of 1 kHz by the "BIOPAC MP35" (BIOPAC systems, Inc., USA). In order to elicit CMAP response, this study used a constant voltage stimulator named "BSLSTMB Stimulator" (BIOPAC systems, Inc., USA). This stimulator can vary the output voltage in the range 0-100 volts. When a stimulus was occurred, the BSLSTMB stimulator would generate a defined constant voltage to the sciatic nerve via bipolar needle electrodes and also sent a trigger signal to the digital input port of BIOPAC MP35. This triggering signal would be used for CMAP responses segmentation later on. The CMAP response would appear on the EMG signals at some latency after stimulus (after trigger). The "BIOPAC BSL 4.0 MP35"software was used for electrical nerve stimulation and signal recording setups, recording and monitoring all acquiring data (EMG, CMAP and trigger). This software was run on the Microsoft OS in the laptop computer. Video and sound were recorded via a webcam synchronously with the signal acquisition time by the BIOPAC BSL 4.0 MP35 software. All of the recorded information could be replayed back for better data observation.

***equal contribution**

Research supported by the National Research Council of Thailand (NRCT) and the Government funding of Mahidol University.

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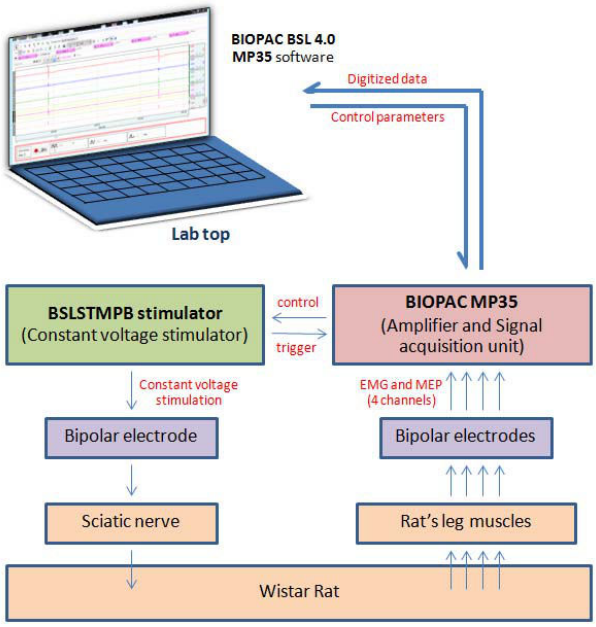

Figure 1. Block diagram of the signal acquisition and electrical nerve stimulation system

B. *Experimental procedure*

When all equipments for signal acquisition and electrical nerve stimulation were completely setup, the experiment was first started on the left sciatic nerve by the sequent as follows;

1. Anesthetized the rat by 80 mg/kg ketamine and 10 mg/kg xylazine and wait until the rat was anesthesia [10].
2. Placed needle electrodes subdermally to the defined locations on the operating leg. The ground electrode was placed at the anterior part of the higher hind limb. These EMG signals were than continuously monitored and recorded by the BIOPAC BSL 4.0 MP35 software.
3. Start surgery to find the sciatic nerve. Figure 2(a) shows the real picture of the sciatic nerve.
4. Record a CMAP response as an initial state condition (Baseline) of the sciatic nerve. This CMAP response could be recorded by applying a lowest voltage (around 0.3 volt) to the sciatic nerve. If there is no CMAP response occurs, then gradually increase that voltage by 0.1 volt until CMAP is appeared. This voltage would be recorded as V_1. Then, apply 5 pulses of V_1, 5 pulses of V_2 (higher than V_1) and another 5 pulses of V_3 (higher than V_2) to the sciatic nerve.
5. Perform a severe irritation by using the forceps press the sciatic nerve until a trauma was occurred (See Figure 2(b)).
6. Record a CMAP response after this irritation by applying 5 pulses of a lowest voltage (V_4) that could elicit the CMAP response, 5 pulses of V_5 (higher than V_4) and another 5 pulses of V_6 (higher than V_5) to the sciatic nerve.
7. Partially cut the sciatic nerve about 50% by the needle No.18, 1½" (see Figure 2(b)).
8. Record a CMAP response after about 50% damage by applying 5 pulses of a lowest voltage (V_7) that can elicits the CMAP response, 5 pulses of V_8 (higher than V_7) and another 5 pulses of V_9 (higher than V_8) to the sciatic nerve.
9. Repeat the sequent number 2-8 to the right side of the rat's sciatic nerve.

After both sciatic nerves were operated, the rat was terminated by injecting 3 times of the anesthetized xylazine [10]. The recorded EMG and trigger data were converted into .mat file for later processing in the MATLAB software (R2008a, the Math Work Inc, USA).

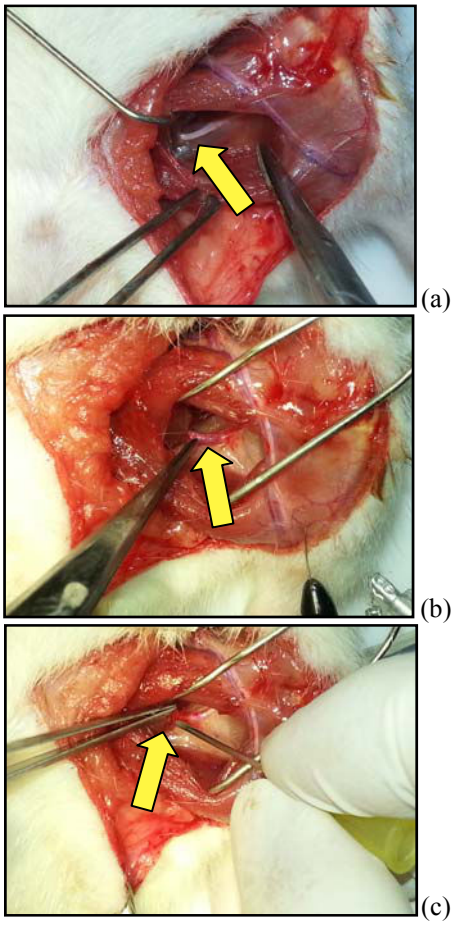

Figure 2. Rat's sciatic nerve; (a) initial state of the sciatic nerve, (b) the sciatic nerve after severe irritation and (c) the sciatic nerve after about 50% of sciatic nerve damage.

C. *Data analysis*

The recorded 4 channels EMG data were filtered by digital highpass filter at cut off frequency of 2 Hz to avoid some direct current (DC) offsets and movement artifacts. In order to obtain the CMAP signal from each stimulus, the EMG signals were segmented accordingly to the trigger data that generated by the stimulator. The 5 CMAP responses that elicited by a particular voltage level (V_1, V_2, …, V_9) were averaged into CMAP1, CMAP2, …, CMAP9 as the grand average of CMAP response at the initial state (CMAP1-3), after severe irritation (CMAP4-6) and after about 50% damage (CMAP7-9), respectively. Then, these grand average CMAP responses were used for calculating a voltage peak-peak (V_{pp}) of each sciatic nerve conditions (initial state; V_{pp1}, V_{pp2} and V_{pp3}, after severe irritation; V_{pp4}, V_{pp5} and V_{pp6}, and after about 50% damage; V_{pp7}, V_{pp8} and V_{pp9}). These V_{pp} values were averaged among 4 channels. TheV_{pp} values would be later used for the sciatic nerve modeling.

D. *Nerve modeling*

Figure 3 shows a block diagram of the nerve model. The constant voltage stimuli were considered as input data (x[n]) whereas output data (y[n]) was a voltage peak-peak (V_{pp}) of the CMAP responses. We hypothesized that when an input voltage was increased, V_{pp} also increased relatively [5]. Therefore, this study considered the nerve response as a linear model (h(x[n])).

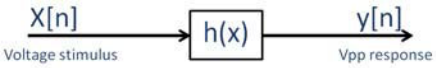

Figure 3. Block diagram of nerve model

Since the nerve was simply considered as a linear model, the hypothesis (h(x)) could be represented as a linear equation as shown in Equation 1.

$$h_\theta(x) = \theta_0 + \theta_1 x = y, \quad (1)$$

Where, θ_0 is the y-axis intersection point and θ_1 is the slope. This two unknown parameters could be calculated by linear least square solution [11] as shown in Equation 2.

$$\theta = (X^T X)^{-1} X^T y, \quad (2)$$

where, $\theta = \begin{bmatrix} \theta_{0\{i\}} \\ \theta_{1\{i\}} \end{bmatrix}$, $X = \begin{bmatrix} 1 & V_{\{i+1\}} \\ 1 & V_{\{i+2\}} \\ 1 & V_{\{i+3\}} \end{bmatrix}$, $y = \begin{bmatrix} V_{pp\{i+1\}} \\ V_{pp\{i+2\}} \\ V_{pp\{i+3\}} \end{bmatrix}$.

Parameter *i* is 0 for initial condition, *i* is 3 for severe irritation condition and *i* is 6 for 50% damage condition.

III. Results

Figure 4 shows an example of grand average of CMAP responses at the initial state of the sciatic nerve. Red, blue and green lines were CMAP responses after stimulated by 0.5 (V_1), 0.7 (V_2) and 0.8 (V_3) volts, respectively. The results revealed that when the stimulating voltage was increased then the CMAP response also increased peak-peak amplitude (V_{pp}). Consequently, the proposed hypothesis of linearly nerve model would be a promising strategy for nerve modeling.

After all parameters were calculated ($V_{1\text{-}9}$ and $V_{pp1\text{-}9}$), the linear model parameters (θ_0 and θ_1) at each sciatic nerve conditions were then determined by the Equation 2. Figure 5 showed an example of voltage peak-peak values of CMAP responses (y-axis) of differences constant voltage (x-axis) at the initial state of the sciatic nerve (o), after severe irritation (□) and after about 50% damage (◊) conditions. This information was then used for calculating θ_0 and θ_1 of nerve model at the initial state (red line), after irritation (blue line) and after about 50% damage (green line) conditions.

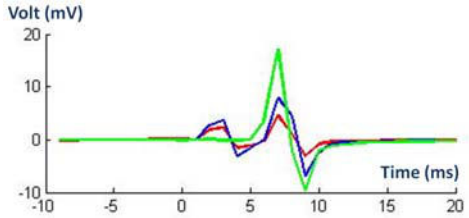

Figure 4. Example of grand average of CMAP responses at the initial condition of sciatic nerve; Red, blue and green lines are the grand averaged of CMAP responses after stimulating by 0.5 (V1), 0.7 (V2) and 0.8 (V3) volts, respectively.

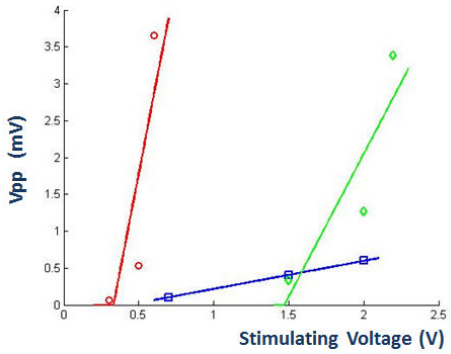

Figure 5. An example of Vpp and stimulating voltage data and linear model of each nerve conditions (of initial state (o, red line), after irritation (□, blue line) and after about 50% damage (◊, green line) conditions).

The results showed that the nerve models calculated from CMAP responses at each nerve conditions were different. The nerve model at the initial state of the sciatic nerve has highest slope (θ_1) and lowest intersection point on y-axis (θ_0) as shown in Figure 6 (a) and (b). About 50% nerve damage (partially cut) condition could decrease θ_1 but increase θ_0. Given a severe irritation to the sciatic nerve could make its slope significantly decreased (pared t-test, $p<0.05$) compared with the baseline (See Figure 6 (a)).

Another indicator would be a stimulating voltage offset. In this study, the stimulating voltage offset was determined by calculating the different of x-axis intersection point between linear model at the initial state to the severe irritation and about 50% nerve damageconditions (See Figure 6 (c)). The results showed that there was a smaller stimulating voltage offset after severe irritation than after about 50% nerve damage condition. This index would also be a promising parameter for predicting the nerve function. Figure 7 showed an averaged linear model of sciatic nerve at the initial state (red o), after severe irritation (blue □) and after about 50% nerve damage (green ◊) conditions. This model was averaged among 4 sciatic nerves (2 Wistar rat).

IV. Discussion

Peripheral nerve injury such as complete or partial nerve damage would result in long-term clinical nerve dysfunction. On the other hand, the surgical manipulation particularly severe irritation, could cause the nerve injured but it could be recovered its function afterward. The recorded spike and burst EMG are commonly used for observing a severity of mechanical irritation level however this could not identify short-or long-term nerve dysfunction [1, 2].

In practice, the uses of CMAP response were emphasized for being a promising indicator for nerve outcome prediction. Regarding the hypothesis, the nerve model is linear, increasing voltage stimulus level will increase amplitude of the CMAP response [5] (See Figure 4). After a few different voltage stimulus levels were applied to the nerve, we could then approximately model the equation and obtain linear equation parameters (θ_0 and θ_1) (See Figure 5). When the sciatic nerve was undergone with severe irritation, θ_0 and θ_1 were increased and significantly decreased, respectively compared with the baseline (See Figure 6 (a) and (b)). About 50% of sciatic nerve damage, there were increased θ_0 and decreased θ_1 but not exactly the same level to severe irritation condition.

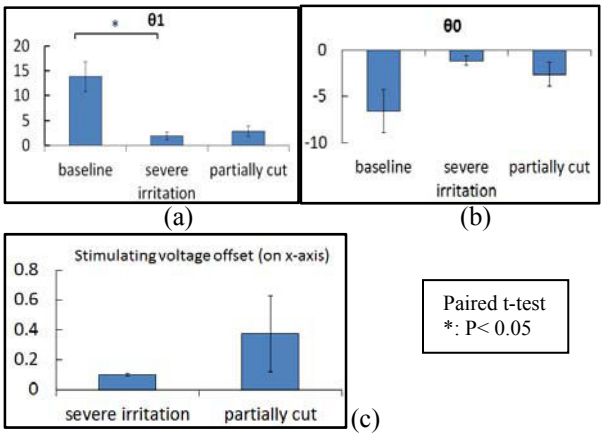

Figure 6. The comparison of parameter θ_0 (a) and θ_1 (b) at each nerve conditions, and (c) the comparison of the different of the stimulating voltage offset (intersection point on x-axis) after baseline condition.

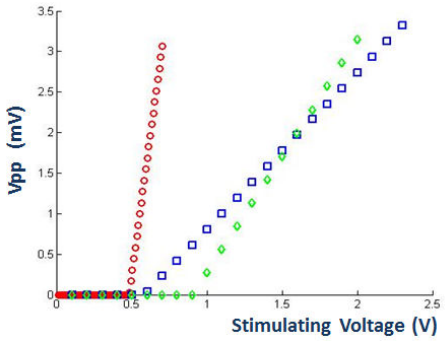

Figure 7. The sciatic nerve model at the initial state (red o), after irritation (blue □) and after about 50% nerve damage (green ◊) conditions.

Another interesting indicator was the stimulating voltage offset. About 50% of sciatic nerve damage, the result showed a higher offset than the severe irritation condition (See Figure 6 (c)). Practically, this result could be used for on-line identifying nerve conditions. Highly decreasing in slope and small change of stimulating voltage offset might be considered as severe irritation state. Conversely, highly change in stimulating voltage offset and small decrease in slope may refer to permanently damage. Generally, more than three sample points would benefit to model fitting. However, correcting numerous samples would be more time consuming for real surgery. In addition, in this present study, there was a small number of the sciatic nerve (n = 4). To increase sample size is also recommended. For further investigation, each type of sciatic nerve damage should be defined in more detail of irritation and damage level e.g. degree of severe irritation level and percentage of sciatic nerve damage.

V. Conclusion

This present study revealed the peripheral nerve model from sciatic nerve in animal study. This is the first study which determined and compared the results after severe peripheral nerve irritation and about 50% of peripheral nerve damage. According to the result, CMAP response was changed concordant to the amount of the stimulus voltage. The nerve model was considered as linear. The linear equation parameters of the nerve model were shifted differently after the peripheral nerve was manipulated with severe irritation and about 50% of peripheral nerve damage. This shifting model could be used for predicting the nerve function (short- or long-term nerve dysfunction). By monitoring of CMAP response on traditional nerve preservation [5-9], this present study shows the new modality for peripheral nerve examination and identifies by shifting of the nerve model.

Acknowledgment

This projected is supported in part by Thailand Center of Excellence for Life Sciences (TCELS) and the Government funding of Mahidol University, Thailand.

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