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On the Activation Threshold of Nerve Fibers Using Sinusoidal Electrical Stimulation

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Abstract - **Carpal Tunnel Syndrome (CTS) diagnosis could be improved by selectively activating different types of nerve fibers traversing the carpal tunnel based on their diameter. The objective of this study was to establish the types of fibers activated by different sinusoidal electrical stimuli. The frequencies selected correspond to those used in an available application known as current perception threshold (CPT). This method has been proposed in the literature to assess the severity of CTS in a patient. CPT operates by varying the amplitude and frequency of stimulating sine wave currents. Subthreshold and supra-threshold responses of nerve fibers were modeled in this study using McNeal's model and Frankanhaeuser-Huxley equations. Simulations were performed in MATLAB to determine the stimulating thresholds for different diameter groups of nerve fibers. The study concluded that large A-β fibers can be activated alone at the 2000Hz frequency, the intermediate A-δ fibers can be activated at the 250Hz frequency in company of A-β fiber activity, and for fibers with diameter less than 2.5µm to be activated at the 5Hz frequency there must be accompanying activity from A-β and A-δ fibers.**

I. Introduction

A. Carpal Tunnel Syndrome

Carpal Tunnel Syndrome (CTS) is a nerve conduction syndrome caused by localized compression of the median nerve at the wrist. In general, CTS is clinically diagnosed using a neurophysiologic testing called Nerve Conduction Study (NCS) [1]. In this test, the examiner places surface electrodes on the skin over median nerve and a stimulator is used to deliver a very small electrical current causing the nerves to fire. The electrical signals produced by nerves and muscles are picked up by recording electrodes placed at a distance from the stimulating electrode, then they are analyzed by a physician. An average sensory conduction velocity (CV) of 45m/s or less indicates the presence of CTS [2], [3].

B. Improvement on Nerve Conduction Study

Most common NCS evaluate the performance of large myelinated nerve fibers as a whole. Selective activation of nerve fibers based on their diameter is not achieved through current NCS techniques. Therefore, an early deficit in the activity of small nerve fibers is likely to go unnoticed since the contribution of large nerve fibers to the compound nerve action potential (CNAP) recorded is more significant than the contribution from small nerve fibers. Also, according to the literature [2], severity of CTS progresses from large nerve fibers to small nerve fibers. In other words, during the early stages of CTS, large diameter nerve fibers are affected and when the severity progresses smaller nerve fibers are affected. A current perception threshold (CPT) technique has been proposed to evaluate the response of different types of afferent nerve fibers [2]-[4]. This paper searches, through a simulation study, for the activation thresholds of nerve fibers being stimulated with the type of sinusoidal electrical waveforms used in the CPT technique.

C. Current Perception Thereshold

The CPT technique uses alternating current of different frequencies for selective stimulation of nerve fibers. Nishimura, et.al [2]-[4] stated that CPT offers the possibility to selectively test A-beta, A-delta and C-fibers. Fibers are classified according to their CV range. A-beta fibers having a CV above 30m/s are the largest fibers that mediate the sensation of touch and mild pressure, as well as positions of joints and muscular vibration. A-delta fibers, smaller than A-beta fibers, have a CV of 2 to 30m/s. They mediate the sensation of cold and the first components of pain sensation. C-fibers, the slowest and the smallest group, have CV less than 2m/s and mediate the sensation of warmth and the main components of the pain sensation. When a patient is affected by CTS, the large fibers are injured first, and subsequently smaller ones are affected, i.e. A-beta fibers are injured by compression, A-delta fibers by ischemia and C-fibers by persistent compression [2].

Quantitative CPT testing with the Neurometer selectively evaluates A-beta, A-delta and C-fibers because the alternating current wavelengths required to stimulate the different nerve fibers depend on fiber diameter [2]. The Neurometer is a portable battery operated trans-cutaneous electrical nerve stimulator which emits constant sine wave stimulation at 2000Hz, 250Hz and 5Hz frequencies graded at digitally calibrated levels of 0 to 10mA [5]. Unmyelinated C-fibers are to be activated by the 5Hz stimulus; thinly myelinated A-delta fibers by the 250Hz stimulation and large myelinated A-beta fibers by the 2000Hz stimulation. It is argued that large diameter fibers respond to rapid 2000Hz stimulus, while small unmyelinated fibers require several milliseconds of continuous depolarization to respond.

Also, large diameter fibers repolarize more rapidly in the presence of the 5Hz sinusoidal waveform stimulation.

II. Method

Simulations were performed in MATLAB to determine the stimulating thresholds required for different diameter of nerve fibers. McNeal's model [6] along with Frankanhaeuser-Huxley equations for the ionic currents [7] were used to model activation of median nerve fibers. McNeal represented a myelinated nerve fiber by an electrical network. The excitation nodes, defined as the nodes at which the excitation will originally occur, can be predicted using the subthreshold response. The membrane at this node is then modeled using Frankanhaeuser-Huxley equations to get an accurate representation of the membrane potential near and above the threshold (suprathreshold response). If the maximum depolarization is the same at two or more nodes, the membrane at each of these nodes is modeled using Frankanhaeuser-Huxley equations [7]. A nerve depth of 6mm under the stimulation electrode was considered.

Stimulating currents consisted of sinusoidal waveforms. The frequency of the sine wave was varied and for each frequency the stimulating thresholds required to activate nerve fibers of different diameters were found. The study was performed for three different sine wave frequencies: 2000Hz, 250Hz and 5Hz [8]. The stimulating thresholds for different fiber diameters were found using the following procedure. A sinusoid of one frequency was chosen at a time. Starting at 0mA, the amplitude of the sinusoidal stimulating current was increased in steps of 0.01 mA and the minimum current required for generating a suprathreshold response in a nerve fiber was found. A suprathreshold or above threshold response to a stimulus is that for which an action potential is generated and the minimum amplitude of the stimulating current needed is known as the stimulating threshold. Nerve fibers with diameters from 2μm to 20μm were considered for this study. This process was repeated for all three frequencies and the results were plotted for analysis. These results are shown in the next section.

III. Results

Using McNeal's nerve fiber model, simulations were performed in MATLAB as discussed. The stimulating threshold required for a nerve fiber with 20μm diameter, using a 250Hz sinusoid, was found to be 2.46mA. The 250Hz stimulating sinusoidal current waveform with peak amplitude of 2.46mA is shown in Figure 1. This is the lowest amplitude of a sinusoidal stimulus with a 250Hz frequency able to elicit APs as the suprathreshold response in Figure 2 shows. Figure 2 shows the membrane potential response of the 20μm nerve fiber to this stimulus. The membrane firing threshold is exceeded in two occasions.

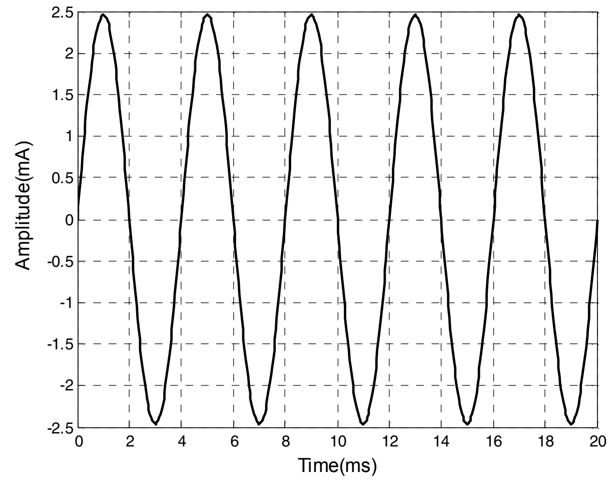

Figure 1. Sine wave stimulating current with a frequency of 250Hz and amplitude of 2.46mA

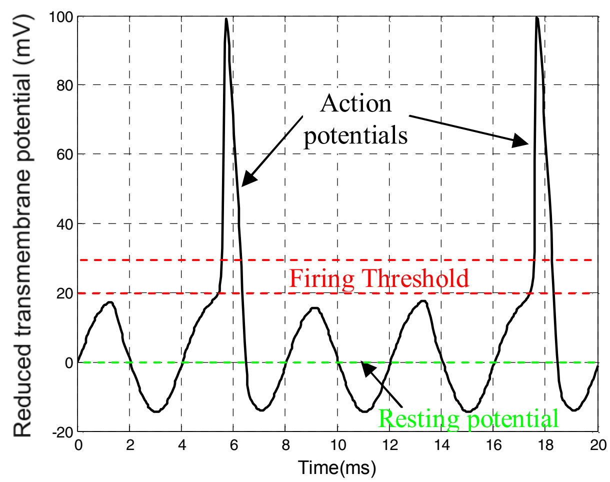

Figure 2. Suprathreshold response of a 20μm diameter fiber when stimulated with the 250Hz sinusoid shown in Figure 1.

Likewise, the stimulating thresholds for different fiber diameters were found for each of the three frequencies; 2000Hz, 250Hz and 5Hz. The stimulating thresholds obtained for all three frequencies were plotted against the corresponding fiber diameter as shown in Figure 3. It can be seen that the stimulating current threshold follows the same monotonically decreasing trend for all three sine wave frequencies.

IV. Discussion

According to Nishimura et. al it is required that the 2000Hz sinusoidal waveform can selectively stimulate large nerve fibers with a CV ≥ 30m/s, *i.e.* fibers with diameter greater than 8μm approximately. It is also required that the 250Hz sine wave can stimulate fibers in the velocity range 3m/s to 30m/s, i.e. fibers with diameter between 2.5μm and 8μm, and finally that the 5Hz sinusoid can be used to stimulate nerve fibers with CV ≤ 3m/s, i.e. nerve fibers with diameter less than 2.5μm.

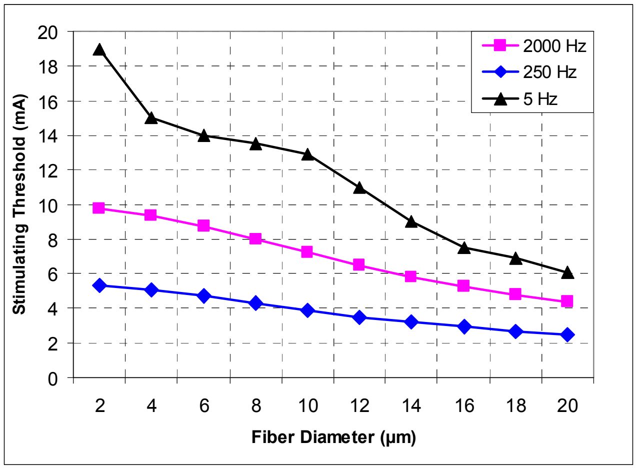

Figure 3. Stimulating threshold vs. fiber diameter for 2000Hz, 250Hz and 5Hz sine wave stimuli

CV is related to fiber diameter through the expression [9]:

$$CV = 4.9\,D - 9.0$$

where D is the fiber diameter in [μm].

The first requirement that the 2000Hz sine wave stimulates large diameter A-β fibers with CV≥30m/s (D≥8μm) while not activating fibers having CV less than this value has been based on large diameter fibers responding to rapid 2000Hz stimulus, while small unmyelinated fibers requiring several milliseconds of continuous depolarization to respond [2]. Fig.3 suggests that this is the case as long as the stimulus amplitude is kept below 8mA, then only fibers with D≥8μm are activated. If the stimulus amplitude is increased above 8mA some activity from A-δ fibers is expected as well.

The second requirement is that the 250Hz sinusoidal stimulating current activates fibers with diameters between 2.5μm and 8μm. Since the stimulation thresholds shown in Fig.3 for fibers with D>8μm are lower than the stimulation thresholds of any fiber in [2,8]μm it means that activating fibers in this range will also potentially activate fibers of larger diameters. This is a consequence of the monotonically decreasing trend of the 250Hz curve. The third requirement that the smallest unmyelinated C-fibers are activated by the 5Hz stimulus and larger diameter fibers not being as sensitive to this stimulus has been based on larger diameter fibers repolarizing more rapidly than required to fire under 5Hz sinusoidal waveform stimulation. According to Figure 3, the smallest fibers (D≤2.5μm) have the highest stimulation threshold, therefore larger A-β and A-δ fibers (D>2.5μm) will also be contributing with some activity under a 5Hz sinusoidal stimulus.

In all three cases, the stimulating threshold follows the same trend, i.e. for any frequency of the sinusoidal stimulating current the larger nerve fibers require smaller current to get activated compared to the smaller nerve fibers. In other words, when the stimulus current amplitude is increased large nerve fibers are activated first, followed by smaller nerve fibers later. These findings are in agreement with results reported from experiments in rats [10], where the firing frequency of each fiber type under each stimulus frequency seems to play an important role for functional stimulation to be achieved.

It is interesting to note in Figure 3 that the threshold current required for exciting nerve fibers using a 250Hz stimulus is less than the current required to activate fibers using a 2000Hz sine wave stimulating current. In other words, nerve fibers are more sensitive to a 250 Hz alternating current (AC) than to a high frequency (2000Hz) AC. This is agreement with the human body, particularly nerves and muscles, being more sensitive to 60Hz AC than higher frequencies or direct current (DC) [11]. Therefore, it is not surprising that nerve fibers have a lower stimulating threshold when a 250Hz sine wave current is applied, which is closer to the 60Hz AC than a 2000Hz high frequency stimulating current, or 5Hz that is close to DC.

V. Conclusion

The CPT technique suggested by Nishimura et. al to selectively stimulate nerve fibers in order to detect the severity of CTS was assessed in this study. All three frequencies used in CPT, 2000Hz, 250Hz and 5Hz, were tested for their capability to independently activate nerve fibers. It was found that, by varying amplitude and frequency of the stimulating sinusoidal current, selective activation of nerve fibers according to their diameter or conduction velocity may not be possible for all three frequencies. In other words, by decreasing the frequency of the sine wave smaller nerve fibers cannot be activated without eliciting activity from larger fibers. All three sine wave frequencies followed the same trend of activating large nerve fibers first followed by smaller nerve fibers as the stimulating current amplitude was gradually increased. Achieving functional stimulation of the different types of afferent nerve fibers in humans grants further research. Further scrutiny into the firing frequency of the different types of fibers under each stimulus frequency is suggested, followed by a comparison with the firing frequency perception thresholds of humans for each fiber type.

VI. References

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