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Counted Cycles Method to Quantify the Onset Response in High-Frequency Peripheral Nerve Block

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***Abstract*— The clinical use of high frequency alternating current (HFAC) to block nerve conduction in peripheral nerves is limited due to the large volley of nerve activity generated at the initiation of HFAC. This "onset response" must be characterized in order to determine if it is possible to eliminate it. In this study, preliminary experiments were conducted in an *in-vivo* animal model using counted cycles of HFAC to investigate and quantify the onset response. Using this method, it is possible to show quantitatively that the onset response has two phases with distinct characteristics. Eliminating the onset response is likely to require addressing each phase independently. It was also possible to show that HFAC establishes a complete block of nerve activity in 50 – 100 ms.**

I. Introduction

A quick-acting and quick-reversing peripheral nerve conduction block would offer potential clinical value in treating diseases marked by pathological hyperactivity of peripheral nerves, including spasticity, movement disorders, and peripheral nerve pain. Current treatment modalities are either short-acting or irreversible and have significant side effects. *In vivo* mammalian experiments have shown that high frequency alternating current (HFAC) applied directly to the nerve produces a quick-acting and quick-reversing conduction block with a minimum of side effects. HFAC waveforms in the frequency range of 1 – 40 kHz, delivered through an electrode encircling the nerve, can produce a local conduction block in a variety of mammalian species and nerve diameters [1] – [8]. The amplitude required to produce a complete conduction block depends on the waveform and waveform frequency, as well as the electrode design and the nerve size. Blocking amplitudes typically range from 1 – 10 Vpp for voltage-controlled HFAC and 1 – 12 mApp for current-controlled HFAC [7], [9]. Normal nerve conduction is restored within one second following termination of the HFAC [1], [3].

At the onset of the HFAC, the nerve response is marked by a train of activity, referred to as the "onset response". This initial response has been observed in animal experiments using single fiber recording [3], [8], muscle force [1], [7], urethral sphincter pressure [2] and in computer simulations [1], [4], [5], [7], [9]. Two sequential phases have been identified to describe the onset response in terms of the force generated in the muscle innervated by the blocked nerve [1], [9] (example in Figure 3). The first phase consists of a single summated muscle twitch with a peak force much larger than that of a normal supramaximal muscle twitch. We have defined this as the "Phase I onset" and it is always present. We define "Phase II onset" as immediately following Phase I and it is a variable period of repetitive firing that ends with complete or partial block. The Phase II response can be eliminated or minimized by optimal electrode placement, higher HFAC frequencies and most importantly by amplitudes higher than block threshold [1].

This paper demonstrates a novel method to quantify the difference between the Phase I and Phase II onset responses and also allows measurement of the time required for the nerve to reach a completely blocked stage. The aim is to obtain temporal information of neural firing from only muscle force measurements. The method, referred to as "the counted cycles method", measures the maximum force and area of the onset response that is generated in the muscle in response to trains of counted cycles of HFAC applied to a motor nerve. *The key maneuver is to perform these train sequences at two amplitudes*, one above the block threshold and the other below block threshold. The supra threshold trains produce an onset that is quickly damped due to the nerve reaching a blocked state (a predominant Phase I response with minimal or no Phase II). The sub-threshold trains permit the full manifestation of both Phases I and II. The difference between the two sets of data allows separation of the two phases. The method also gives insight into the time it takes for a complete nerve block to occur. While previously measured in HFAC motor nerve block from muscle twitch data, that is a measure of the time that the *muscle* needs to stop responding following nerve block. That time is vastly greater than the time it takes for the *nerve* to stop firing and reach a blocked state. The counted cycles method allows the experimental measurement of this time in mammalian nerves at a fine temporal resolution (0.05 ms for a HFAC at a frequency of 20 kHz).

II. Methods

A. Animals and Surgical Procedure

The onset response was evaluated using a muscle–nerve preparation in adult rats (~400 grams) (Sprague-Dawley). All protocols involving animal use were approved by the

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institutional animal care and use committee. The rats were anesthetized with intraperitoneal injections of pentobarbital sodium (Nembutal). One hind leg was shaved, and an incision was made along the caudal aspect of the thigh and leg. The gastrocnemius–soleus muscle was exposed and the calcaneal tendon divided and clamped. The sciatic nerve was exposed from 1 cm lateral to the spine to its terminal branching into tibial and peroneal nerves. The sural nerve was cut. The animal was stabilized on a customized fixture with a clamp on the ipsilateral tibia. The tendon clamp was connected to an in-line force transducer (Entran, Fairfield, NJ) to measure isometric muscle force (resolution 0.005 N). Experiments were performed on five animals. The results from one animal are presented in this paper.

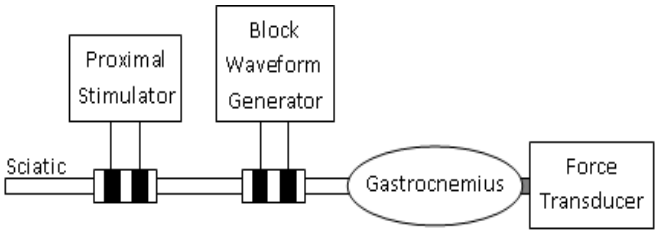

Fig. 1. Illustration of the experimental setup showing the position of the stimulating and blocking electrodes along the sciatic nerve.

B. Electrical Stimulation and Block

Two bipolar platinum cuff electrodes were positioned along the nerve about 1 cm apart, as illustrated in Figure 1. The proximal electrode was used to deliver an electrical test stimulus from an isolated square pulse stimulator (Model S88, Grass Technologies) to maximally excite the gastrocnemius muscle. The distal electrode, positioned between the proximal electrode and the muscle, was used to deliver the HFAC (20 kHz) from an isolated voltage-controlled function generator (Model 395, Wavetek). A Labview program controlled the Wavetek to produce a train of counted cycles.

C. Experimental Protocol

The experiments began by first determining the block threshold, or the minimum HFAC amplitude required to maintain a complete conduction block, for the voltage-controlled 20 kHz sinusoidal HFAC waveform. This amplitude was then used to select the sub-block threshold and supra-block threshold amplitudes to be used for the HFAC train. For the preliminary experiments, a sub-block threshold amplitude of 5 Vpp and a supra-block threshold amplitude of 10 Vpp were used.

Once the block threshold was determined and the HFAC amplitudes were selected, a series of trials were collected delivering a train of HFAC with increasing cycle counts ranging from 1 to 50,000 cycles. The amplitude of the HFAC trains for each trial were randomly chosen between the two amplitudes selected, 5 Vpp or 10 Vpp (for a total of 3 repeats per amplitude). At the beginning of each trial, three to four proximal test pulses were delivered to the nerve to obtain a consistent measure of the muscle twitch for comparison to the onset responses from each HFAC train.

The maximum force and area of the onset response was calculated for every trial. Occasionally the HFAC generated a muscle twitch at the end of the train, termed an off

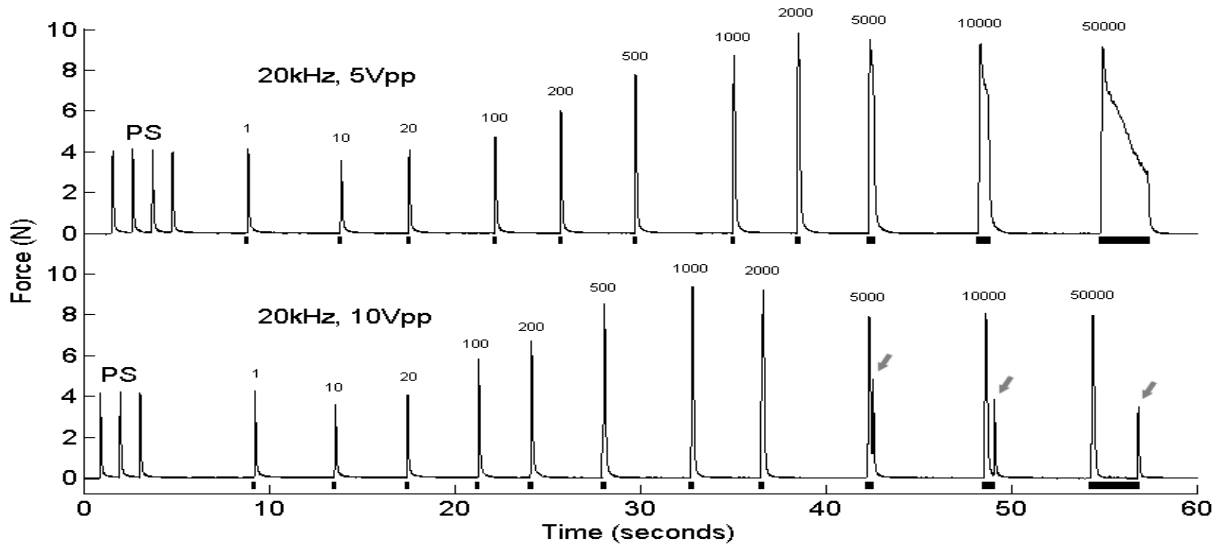

Fig. 2. Two representative trials showing the gastrocnemius force response to trains of counted cycles of HFAC at sub-block threshold (*Top*) and supra-block threshold (*Bottom*) with consecutively increasing cycles (the measured block threshold at 20 kHz was 7 Vpp). Solid black bars indicate the timing of each HFAC train. Trials began with 3 – 4 twitches elicited from the proximal test stimulus (PS), followed by 1, 10, 20, 100, 200, 500, 1,000, 2,000, 5,000, 10,000, and 50,000 cycles of 20 kHz HFAC (indicated on top of each muscle response). The onset response is similar to a single muscle twitch for cycle counts less than ≤ 20 (=1 ms). The peak force of the onset increases with increasing cycle count until 1000 to 2000 cycles. The area under the force curve keeps increasing for sub-block threshold trains (*Top*) but reaches a maxima (indicating complete block) for the supra-block threshold trains (*Bottom).* Grey arrows indicate a short response when the HFAC block turns off (off response).

response (Figure 2 grey arrows). This off response twitch was not included in the area calculation.

III. Results

A. Onset Response and Repetitive Firing

The onset response produced by the HFAC train showed a typical response pattern, including the initial Phase I onset response and the repetitive firing of Phase II as described previously [1], [9]. Figure 2 shows the onset response generated by the trains of consecutively increasing cycle counts at both HFAC amplitudes. The first four twitches of the 5 Vpp trial and the first three twitches of the 10 Vpp trial are single muscle twitches elicited by the proximal test stimulus (PS). The number of complete cycles used for each HFAC train in Figure 2 is indicated above the respective onset response and ranges from 1 cycle to 50,000 cycles.

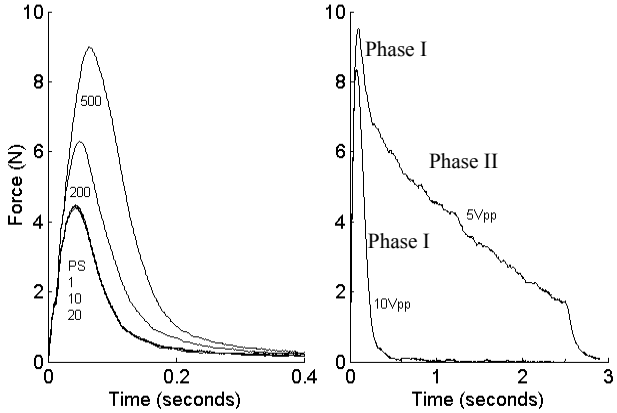

Fig. 3. (*Left*) The onset responses of 10 Vpp HFAC trains consisting of 1, 10, 20, 200, and 500 complete cycles are plotted on top of each other along with a single twitch from the proximal stimulation (PS) to show the single twitch onset response for cycle counts 1 to 20 and the summated twitch onset response for longer cycle counts. (*Right*) Overlay of the 5 Vpp and 10 Vpp onset response for 50,000 cycles of 20kHz HFAC (note different time scale). This comparison illustrates the difference between a Phase 1 only onset at higher HFAC amplitudes and the Phase 2 onset of the lower amplitude HFAC showing ongoing repetitive firing.

Phase I occurred immediately after the block waveform was turned on and varied from a single muscle twitch to a summated twitch response with an increased peak force and duration. The shortest onset response was produced by cycle counts less than 100 and had a peak force and duration equal to a single muscle twitch. The left panel of Figure 3 compares a single twitch elicited by the proximal test stimulus (PS) to the onset responses shown in Figure 2 for 10 Vpp HFAC trains with cycle counts of 1, 10, 20, 200, and 500. The responses to cycle counts of 1, 10, and 20 are identical to the single twitch, while the responses to 200 and 500 cycles are summated twitches with peak force values 1.7 and 2 times that of a single twitch, respectively.

Phase II of the onset response consisted of a period of repetitive firing. The prolonged onset response in response to the 5 Vpp HFAC trains shown in Figure 2 includes the Phase II repetitive firing. The short-duration onset response in response to the 10 Vpp HFAC trains, however, does not show Phase II firing. The right panel of Figure 3 compares the onset responses to 50,000 cycles for both the 5 Vpp and 10 Vpp HFAC. The onset response of the 5 Vpp HFAC train lasts the duration of the train, 2.5 seconds, whereas the response to the 10 Vpp HFAC train lasts only 500 ms.

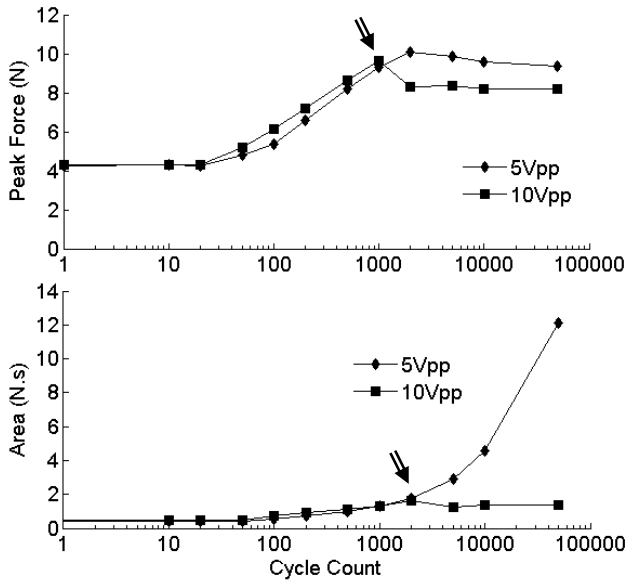

Fig. 4. Peak force (*Top*) and area (*Bottom*) measurements averaged over multiple trials comparing the onset response for different cycle counts with both the sub-block threshold, 5 Vpp, and supra block threshold, 10 Vpp, HFAC amplitudes. (*Top*) The peak force of the onset response increases with increasing cycle count until 2,000 cycles, beyond which the peak force decreases slightly. (*Bottom*) The area of the onset response continues to increase with cycle count for the 5 Vpp HFAC amplitude due to the continued repetitive firing during Phase II. At 10Vpp, however, the area does not increase beyond HFAC trains of 2,000 cycles as only Phase I of the onset is present and the nerve has reached complete block. Arrows show bifurcation points.

B. Quantification of Block Onset

The maximum force and area of the onset response was calculated for each HFAC train. The average maximum peak force and area measurements from multiple trials were plotted as a function of the cycle count for each train of HFAC, shown in Figure 4. Peak force increases with increasing cycle count and reaches a plateau after 1000 cycles (equivalent to 50 ms). Following this there is a moderate difference between complete block (suprathreshold amplitude) and none or incomplete block (sub threshold amplitudes). The former tends to be approximately 10 % lower. The area measurement reveals a more dramatic difference. Areas are similar for different cycles for both amplitudes. With sub threshold amplitudes the area of the onset continues to increase with increasing cycle count. At the supra block threshold amplitudes, the area reached a plateau after 2,000 cycles (equivalent to 100 ms). The two bifurcation points (black arrows in Figure 4) give a range estimate of the time it takes for the nerve to reach complete block. In this series this time is in the order of 50 to 100 ms.

IV. Discussion

The use of HFAC as a quick-acting and quick-reversing peripheral nerve conduction block shows promise for the potential treatment of diseases marked by undesirable pathological hyperresponse of peripheral nerves. However, before HFAC can become a clinically viable treatment, the onset response must be addressed. This study has taken a new approach to evaluating and quantifying the onset response in an effort to better understand the phenomenon and ultimately design methods to minimize this undesired response and quantify the reduction in the onset.

The counted cycles method allows us to clearly differentiate between the Phase I and II responses in any HFAC nerve block test. We hypothesize that any attempt to eliminate the onset response will have to separately address Phase I and II, since it is likely that these two phases arise from different mechanisms. In ongoing experiments in our laboratory, we already have evidence that the electrode design strongly affects Phase II, but has little effect on Phase I. It may be possible to completely eliminate the Phase II onset through proper electrode design alone. However, we expect that Phase I can only be eliminated through significant modification of the HFAC waveform. The counted cycles method allows quantification of the duration of Phase I in millisecond to sub-millisecond resolution, providing an excellent outcome measure to compare the effectiveness of waveform modifications in the future.

The counted cycles method allows measurement of the time taken by the nerve to reach a completely blocked state with a one millisecond temporal resolution. The method was designed to exploit the behavior of the nerve to sub and supra block threshold HFAC. The achievement of complete block in the latter resulted in cessation of nerve firing. While this is discernible in the muscle force record, force data alone does not easily transform to an estimation of the timing of individual action potentials. The use of sequenced counted pulses allows us to know exactly how long the nerve was exposed to the HFAC (in millisecond or sub-millisecond time). The recorded muscle response from a series of counted cycles can be correlated with the HFAC exposure time, providing a direct measure of the true time required for the action potentials to cease, i.e. for the nerve to be completely blocked. Conduction block timing can be easily identified as the point where subthreshold and suprathreshold curves diverge, as shown in Figure 4.

The data presented gives an estimate of 50 to 100 ms for the time to achieve complete block. Previous modeling data in a mammalian axon model [9] suggested a time to achieve block of 10 to 30 ms. We hypothesize that the Phase I response is not identical across all experiments. The duration of the Phase I response may vary in the 10s of milliseconds range. Additional experiments are necessary to estimate the variability of the Phase I duration.

We previously postulated that Phase II is affected by many variables, such as the type of electrode, electrode placement, surgical preparation, and other experimental variables. We postulate that the same is true for the Phase I, the difference being that the Phase I occurs within a maximum time of approximately 100 ms while Phase II can last for many seconds.

We have previously shown the amplitude-frequency relationship of the onset response [1]. Higher frequencies and higher amplitudes lead to smaller onsets. However, this relationship was strongly influenced by the long Phase II response. We did not have a method to quantify the Phase I response at that time. The present series of measurements was performed at 20 kHz. Future experiments will explore a range of frequencies and will reveal the relationship of the Phase I response as a function of HFAC frequency. This knowledge has important applications for targeted elimination of the onset response.

References

[1] N. Bhadra, K.L. Kilgore, “High-frequency electrical conduction block of mammalian peripheral motor nerve,” Muscle Nerve, vol. 32, pp. 782–790, 2005.

[2] N. Bhadra, N. Bhadra, K.L. Kilgore, K.J. Gustafson, “High frequency electrical conduction block of the pudendal nerve,” J. Neural. Eng., vol. 3, pp. 180–187, 2006.

[3] B.R. Bowman, D.R McNeal, “Response of single alpha motorneurons to high-frequency pulse trains. Firing behavior and conduction block phenomenon,” Appl. Neurophysiol., vol. 49, pp. 121–138, 1986.

[4] K.L. Kilgore, N. Bhadra, “Nerve conduction block utilising highfrequency alternating current,” Med. Biol. Eng. Comput., vol. 42, pp. 394–406, 2004.

[5] C. Tai, W.C. de Groat, J.R. Roppolo, “Simulation of nerve block by high-frequency sinusoidal electrical current based on theHodgkin-Huxley model,” IEEE Trans. Neural. Syst. Rehabil. Eng., vol. 13, pp. 415–422, 2005c.

[6] J.A. Tanner, “Reversible blocking of nerve conduction by alternating current excitation,” Nature, vol. 195, pp. 712–713, 1962.

[7] R.P. Williamson, B.J. Andrews, “Localized electrical nerve blocking,” IEEE Trans. Biomed. Eng., vol. 52, pp. 362–370, 2005.

[8] M.Y. Woo, B. Campbell, “Asynchronous firing and block of peripheral nerve conduction by 20 Kc alternating current,” Bull. Los Angel Neuro. Soc., vol. 29, pp. 87–94, 1964.

[9] N. Bhadra, E.A. Lahowetz, S. Foldes, K.L. Kilgore, “Simulation of high-frequency sinusoidal electrical block of mammalian myelinated axons.” J Comput Neurosci., vol. 22, pp. 313–326, 2007.