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Reduction of the Onset Response in High Frequency Nerve Block with Amplitude Ramps from Non-Zero Amplitudes

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***Abstract*—High frequency alternating current (HFAC) waveforms reversibly block conduction in mammalian peripheral nerves. The initiation of the HFAC produces an onset response in the nerve before complete block occurs. An amplitude ramp, starting from zero amplitude, is ineffective in eliminating this onset response. In fact, it makes the onset worse. We postulated that initiating the ramp from a non-zero amplitude would produce a different effect on the onset. This was tested in an in-vivo rat sciatic nerve model. HFAC was applied at supra block threshold amplitudes and then reduced to a lower amplitude (0%, 25% 50 %, 75% and 90% of the suprathreshold amplitude). The amplitude was then increased again to the original supra block threshold amplitude. This normally produces a second period of onset response if increased as a step. However, an amplitude ramp was successful in eliminating this onset. This was always possible for the ramps up from 50%, 75 % and 90% block threshold amplitude, but never from 0% or 25% of the block threshold amplitude. This maneuver can potentially be used to maintain complete nerve block, transition to partial block and then resume complete block without initiating another onset.**

I. Introduction

Pathological hyper-activity of neurons occurs in many diseases and results in undesired motor or sensory effects. Blocking this nerve activity could help alleviate pain or stop unwanted motor effects such as muscle spasms and spasticity. High-frequency alternating currents (HFAC), applied to the peripheral nerves, produces a rapid and reversible conduction block with a minimum of side effects [1]-[5]. Existing methods for treating these conditions all have disadvantages and are not consistently successful. HFAC nerve block offers an attractive alternative.

One of the characteristics of HFAC block is the short burst of neuronal firing when the block is first initiated. This activity has been termed the onset response and is undesirable for clinical applications [1]-[6]. Our laboratory has been studying various methods to eliminate or reduce this onset response. One method that has been suggested is a slow increasing amplitude ramp of the HFAC [7]. We have previously shown that an amplitude ramp starting from zero amplitude not only fails to eliminate the onset response but in fact makes it worse [8].

We postulated that an amplitude ramp that did not start from zero amplitude would show a different behavior. HFAC block allows partial block of peripheral nerves when the amplitude of the blocking waveform is lowered [4], [5]. We envision a scenario where the block is turned on (with an initial onset response), and then the block is graded between periods of complete block and partial block, depending on the application. However, to transition from partial to complete block requires increasing the HFAC amplitude which produces another new burst of onset response if done as a simple step function. We postulated that this transition could be accomplished without producing an onset response by using a ramped amplitude starting from a non zero amplitude level. This paper describes our experimental investigation of this postulate.

II. Methods

Acute experiments were performed in adult Sprague-Dawley rats. All protocols involving animal use were approved by our institutional animal care and use committee. The animals were anesthetized with intraperitoneal injections of Nembutal (Pentobarbital sodium). The left hind leg was shaved and an incision was made along the posterior aspect of the leg and thigh. The sciatic nerve was exposed. The common peroneal and sural nerves were severed. The gastrocnemius-soleus muscle complex was dissected, and the calcaneal (Achilles) tendon was severed from its distal attachment. The ipsilateral tibia was stabilized to the experimental rig via a clamp, and the calcaneal tendon was tethered to a force transducer with 1-2 N of passive tension (Figure 1).

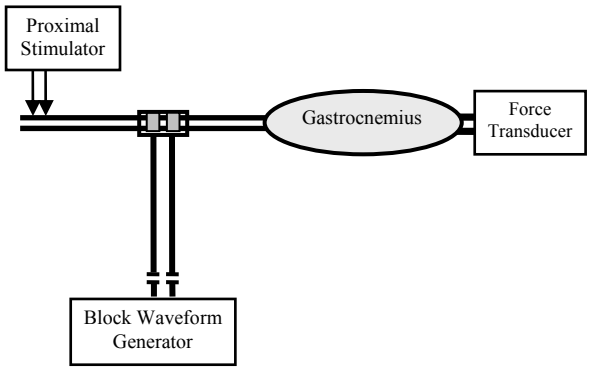

Figure 1.Experimental setup showing the block electrode on the sciatic nerve and proximal nerve stimulation. Force is recorded from the muscle.

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Two nerve cuff electrodes were placed on the sciatic nerve (one shown in Figure 1). Both were bipolar J-shaped silastic nerve cuff electrodes with 3mm x 1mm rectangular platinum contacts [4]. The proximal electrode was used to generate gastrocnemius muscle twitches with the delivery of 1 Hz, 20 μs, supramaximal (typically 300 - 500 μA) cathodic pulses. These pulses were delivered using a Grass S88 stimulator (Grass Technologies) with An isolated current-controlled output stage. The distal electrode was used to deliver the blocking waveform (20 kHz sinusoidals) from a voltage controlled waveform generator (Model 395, Wavetek) with 3 μf capacitors to eliminate any DC offsets. Labview® software controlled the waveform generator and modulated the output to obtain specific ramps as desired. Data sampling rate was 1000 Hz.

A typical trial consisted of proximal stimulation at 1 Hz to get a twitch response. The HFAC, at 20 kHz, was then turned on at 125% block threshold amplitude (**Amp_1**) (block threshold measured in a separate trial). After an initial onset response, complete block was obtained. After 10 seconds, the block amplitude was turned down to one of 5 sub threshold amplitudes (**Amp_2**) (0%, 25%, 50 %, 75 % or 90% of the initial threshold amplitude). This period of HFAC produced reduced or no block. Following this the amplitude was turned back to 125% of the threshold amplitude (**Amp_3**). If done without a ramp, this produced a second onset response. Further trials were done where this transition was an amplitude ramp. The maximum ramp time tested was 30 s. A goal directed search of ramp times (T_ramp) was carried out to find the minimum ramp time that did not produce this second onset (if possible). The aims were: 1. To establish if the second onset could be eliminated with a ramp. 2. Determine if the onset elimination depended on the Amp_2 amplitude. 3. Find the minimum ramp times.

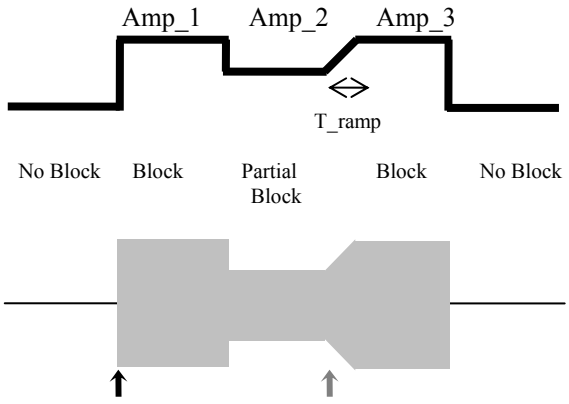


Figure 2. Upper trace shows the control signal from Labview® with the three amplitude zones and the ramp. Lower trace shows the HFAC output. The black arrow points to onset when the HFAC is first turned on. The grey arrow points to where onset occurs during the transition from Amp_2 to Amp_3, which is eliminated by the ramp.

Figure 3. Stacked plot with proximal stimulation running throughout the trials. Each top trace is force, bottom trace is the amplitude control waveform. Black arrows show onset at start of HFAC. Top two traces (A,B) show 0% block during Amp_2 of 50%. Bottom two traces (C,D) show ~60% block during Amp_2 of 75%. No ramp from Amp_2 to Amp_3 produces an onset response (Grey arrows) (A, C). Ramps eliminate this onset (B,D).

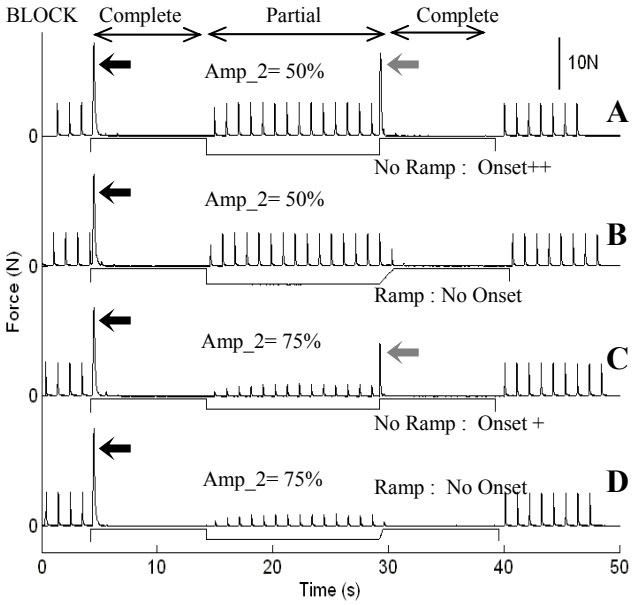
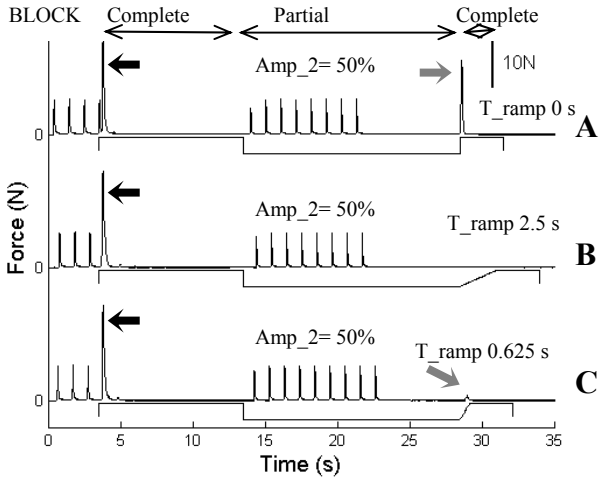


Figure 4. Stacked plot with proximal stimulation running only until ~23 s. Amp_2 is 50 % for all three trials. Each top trace is force, bottom trace is the amplitude control waveform. Black arrows show onset at start of HFAC. Onset occurs for T_ramp of 0 s and 0.625 s (grey arrow). Onset is eliminated for T_ramp of 2.5 s.



III. RESULTS

Complete block was consistently obtained at 20 kHz. The block threshold was measured [4] and 125% of this value used for Amp_1. There was always an onset response at the start of Amp_1 (black arrows in all figures). No onset responses occurred during the transition to the lower amplitude of Amp_2. Different degrees of partial block or no block were obtained during this period of Amp_2 (Figures 3,4,5,6). This depended on the amplitude level of

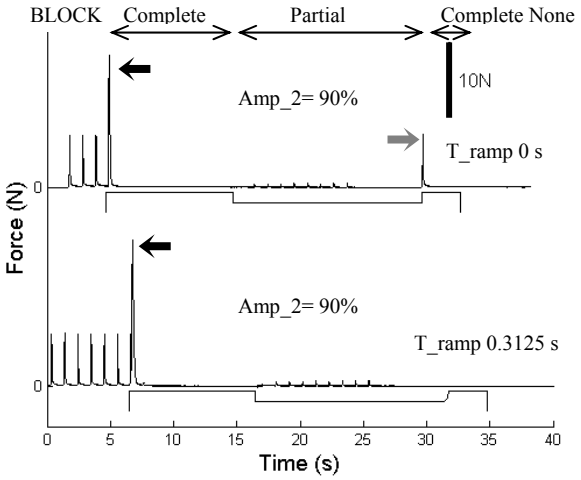


Figure 5. Stacked plot with proximal stimulation running until ~26 s. Amp_2 is 90 % for both trials. Each top trace is force, bottom trace is the amplitude control waveform. Black arrows show onset at start of HFAC. There is ~95% block during Amp_2. No ramp from Amp_2 to Amp_3 produces an onset response (Grey arrow) (upper). A ramp eliminates this onset (lower). T_ramp times are shown.

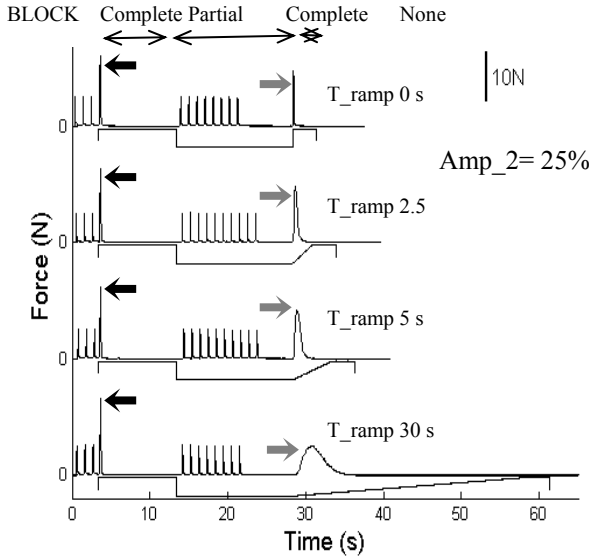


Figure 6. Stacked plot with proximal stimulation running only until ~23 to 25s. Amp_2 is 25 % for all trials. Each top trace is force, bottom trace is the amplitude control waveform. Black arrows show onset at start of HFAC. There is 0% block during Amp_2.There is an onset for the no ramp and the onset response is progressively increased and prolonged with longer ramps. T_ramp times are shown.

Amp_2. For example, Amp_2 of 90% led to almost complete block (Figure 5). Amp_2 of 50% led to almost no block (Figures 3and 4). Amp_2 of 25% led to complete absence of block (Figure 6). Figure 3 shows trials where the proximal stimulation was left on throughout the trial. This shows partial block during the Amp_2 phase and resumption of complete block during Amp_3. It also shows recovery from the block in the time duration following Amp_3.

The transition from Amp_1 to Amp_3 always had a second onset response if this transition was a step function (grey arrows in Figures 3 A & C, 4 A & C, 5 A). An amplitude ramp could eliminate this second onset (Figures 3 B and D, 4 B, 5 lower). Elimination with an amplitude ramp was successful when Amp_2 was 90%, 75% or 50% of the initial Amp_1. However, ramping the amplitude did not eliminate the second onset when Amp_2 was 25% or 0 %. The longer the ramp the more prolonged the onset became (Figure 6).

The T_ramp needed to eliminate the onset was influenced by the level of Amp_2. Higher levels of Amp_2 needed short ramps to eliminate the onset. For example, the minimum ramp times were 0.3125 s for Amp_2 of 90% (Figure 5) and 2.5 s for Amp_2 of 50% (Figure 4 C). Figure 4 C also demonstrates that a shorter ramp (0.625 s) can reduce the onset while a longer ramp (2.5 s) eliminates it (Figure 4 B).

IV. Discussion

An amplitude ramp from zero amplitude fails to eliminate the onset produced in HFAC block of peripheral mammalian nerve. This occurs because the amplitude ramp enters the amplitude zone where the charge in each cathodic half-cycle is sufficient to produce an action potential. Therefore, as the amplitude transitions through this zone, there is a burst of action potentials before the nerve reaches a non-firing steady state. Further increase in the HFAC amplitude eventually produces block [6].

We have shown in this paper that it is possible to transition from a partially blocked state to a completely blocked state without producing an onset response. A ramp from 50%, 75% or 90% of the block threshold amplitude can regain complete block without a second onset response. This occurs because the nerve is maintained in a dynamic steady state by the sub-block threshold amplitude during Amp_2 and this state is above the point at which firing occurs for a ramp starting from zero amplitude. For Amp_2 of 25%, the state is clearly below this firing point. Therefore, amplitude ramps behave similarly to that shown by ramps starting from zero [8]. This implies that there is a certain threshold amplitude above which an amplitude ramp will work. Our present set of experiments was performed with a resolution of 25% of the block threshold amplitude. One of the goals was to demonstrate that the HFAC could be turned down sufficiently to produce no block before turning it back up to full block without an onset. This was achieved in the trials where Amp_2 was 50% (Fig 3, 4).

There are two other trends shown by the data. First, the minimum ramp time that eliminates the onset depends on Amp_2. The further Amp_2 is from Amp_1 the longer the ramp needs to be to eliminate the onset. Second, the onset produced by the transition from Amp_2 to Amp_3 in the no ramp cases was affected by the level of Amp_2. When Amp_2 was higher, the second onset was smaller than the initial onset at Amp_1. This occurs because a higher Amp_2 maintains a larger population of axons in the blocked stage. A transition to Amp_3 only fires the remaining unblocked axons. With a lower Amp_2, more axons are in the unblocked state and they all fire during the transition leading to a larger second period of the onset response.

We believe that the response to ramps from a non-zero amplitude could be a potential method to manage some situations in future clinical use of HFAC nerve block. The experiments described are being repeated in more animals to obtain a statistically significant estimate of the minimum ramp times necessary as a function of the amplitude level during Amp_2.

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