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Conduction block of whole nerve without onset firing using combined high frequency and direct current

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Abstract

This study investigates a novel technique for blocking a nerve using a combination of direct and high frequency alternating currents (HFAC). HFAC can produce a fast acting and reversible conduction block, but cause intense firing at the onset of current delivery. We hypothesized that a direct current (DC) block could be used for a very brief period in combination with HFAC to block the onset firing, and thus establish a nerve conduction block which does not transmit onset response firing to an end organ. Experiments were performed in rats to evaluate (1) nerve response to anodic and cathodic DC of various amplitudes, (2) degree of nerve activation to ramped DC, (3) a method of blocking onset firing generated by high frequency block with DC, and (4) prolonged non-electrical conduction failure caused by DC delivery. The results showed that cathodic currents produced complete block of the sciatic nerve with a mean block threshold amplitude of 1.73 mA. Ramped DC waveforms allowed for conduction block without nerve activation; however, down ramps were more reliable than up ramps. The degree of nerve activity was found to have a non-monotonic relationship with up ramp time. Block of the onset response resulting from 40 kHz current using DC was achieved in each of the six animals in which it was attempted; however, DC was found to produce a prolonged conduction failure that likely resulted from nerve damage.

Keywords

Mammalian peripheral nerve; Nerve conduction block; High frequency alternating current; Direct current; Onset response; Nerve damage

1 Introduction

High frequency alternating current (HFAC), when applied directly to a peripheral nerve, can produce a rapid conduction block that is quickly reversible [8, 11, 23, 41, 42]. Typical parameters utilized to produce this type of block are a 3–40 kHz sinusoidal wave at 3–10 V_{peak-peak} (or 1–10 mA for current controlled studies) [1, 3, 8–10, 16, 38, 41]. This type of block could be useful in treating pain and spasticity. However, HFAC induces a brief but intense burst of axonal firing when HFAC is first delivered to the nerve. This firing is referred to as the “onset response” and is undesirable since it results in a very large contraction in the muscles innervated by nerve being stimulated [8]. In this article we describe a method for eliminating the onset response that utilizes a combination of HFAC and direct current (DC) block to achieve conduction block without the transient contraction which results from the onset response firing.

The onset response generated by the delivery of HFAC consists of a large summated twitch which is usually followed by a period of repetitive firing. There are two distinct phases of the onset response [2, 4, 8, 15, 30, 33]. Phase I is characterized by high firing rate and lasts for approximately 50–100 ms. Phase I is always present regardless of the specific parameters used for HFAC block [4]. Phase II is characterized by a decaying repetitive firing and has a widely variable duration from a few tens of milliseconds to more than 30 s [3, 4, 8, 9, 11, 21, 23, 30, 33, 38, 41, 42]. The duration and intensity of Phase II firing is strongly influenced by waveform frequency [8, 9, 16, 21, 30, 38], waveform amplitude [2, 8, 9, 11, 16, 33], and electrode geometry [4]. We have recently shown that optimized electrode designs can significantly shorten, and in many cases eliminate, Phase II of the onset response [4]. However, it is not possible to eliminate Phase I of the onset response through adjustment of the frequency, amplitude, or electrode design. Therefore, we propose to allow the onset response to occur, but to block it from traveling along the nerve so that it does not reach an end organ or the central nervous system.

DC, when delivered near a nerve at the appropriate amplitude, can produce a complete block of nerve conduction [7, 13, 26–28, 31, 32, 34, 43]. This type of block has been used in many basic and applied research studies and is reviewed by Bhadra and Kilgore [7]. DC block, however, has two contrasting features to HFAC block. First, DC is inherently unsafe to the nerve (and electrode) for chronic use [19, 27, 29, 40]. HFAC, which delivers a zero net charge to the tissue, is likely to be much safer for chronic use, although chronic in vivo testing remains to be completed. Second, it has been shown that DC block can be produced without any onset firing by ramping it from zero to the necessary amplitude for block [31, 43]. Activation at the cessation of DC block (due to anodic break excitation [7, 25]) can be prevented using a ramped [31] or decaying phase [37, 43] after the pulse. Amplitude ramps do not work for HFAC block, and in fact have been demonstrated to exacerbate the onset response [30].

This study represents, for the first time, a particular strategy to approach the problem of the onset response in HFAC: using a separate, brief block (using DC) to stop the HFAC onset response from propagating. In this article, we investigate the general characteristics under which DC block can be accomplished without producing onset activation of its own. Preliminary results for this study have been published in abstract form [24].

2 Methods

Four sets of experiments were performed in this study in a total of 17 adult Sprague-Dawley rats: measurement of DC block threshold (17 rats), measurement of nerve activation during

ramped DC waveforms (6 rats), block of whole nerve using combined HFAC and DC (6 rats), and measurement of nerve conduction failure after repeated DC delivery (5 rats).

2.1 Surgical preparation and experimental setup for nerve block

The surgical preparation was similar to that previously described in other HFAC studies in rat [1, 8, 30]. All protocols involving animal use were approved by our institutional animal care and use committee. The animals were anesthetized with 50 mg/kg initial intraperitoneal injections of Nembutal (pentobarbital sodium). Anesthesia was maintained with 25 or 12.5 mg/kg Nembutal injections based on regular monitoring to ensure a lack of any eye-blink or withdrawal reflexes. The left hind leg was shaved and an incision was made along the posterior aspect of the hind leg and thigh. The sciatic nerve was exposed from its most proximal aspect, just distal to the sacral plexus, to the popliteal fossa. 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 at the heel. Alpha motor fibers in the rat sciatic which innervate these muscles range from 2 to 13 μm in diameter (approximately 200–1600 cm/s conduction velocity) [17, 36]. 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. Mineral oil was applied to the gastrocnemius-soleus muscle complex to prevent it from becoming dry during the experiment.

Figure 1 shows a diagram of the experimental setup. Two or three electrodes were placed on the sciatic nerve as shown in the figure (the HFAC blocking electrode was only present during those trials for which HFAC was delivered). All electrodes were silicone nerve cuffs with a J-shaped cross section and $3 \times 1 \text{ mm}^2$ rectangular platinum contacts for current delivery (the 1-mm dimension was along the longitudinal axis of the nerve) [1, 8, 30]. The proximal electrode was used to generate gastrocnemius-soleus muscle twitches with the delivery of 1.0 or 1.5 Hz, 20 μs supramaximal (typically 300–700 μA) cathodic pulses. These pulses were delivered using a Grass S88 (Grass Technologies, West Warwick, RI, USA) stimulator with a current-controlled output stage. This electrode was bipolar with a 2.0-mm edge-to-edge contact spacing. The proximal stimulating electrode was placed on the sciatic nerve within 1 cm of the sacral plexus.

A monopolar cuff electrode was used to deliver blocking DC. A monopolar electrode was chosen instead of a multipolar electrode because of space considerations on the sciatic nerve. A bipolar DC blocking electrode requires a large surface area for the return contact to prevent nerve activation [31] and would not have easily fit on the nerve preparation with the other electrodes. The monopolar DC electrode was constructed with 1.0 mm of silicone between the edge of the outer platinum contact and each edge of the cuff. A 100- Ω resistor was placed in series with this electrode to monitor DC flowing through it during each experiment, as shown in Fig. 1. An Ag|AgCl gel monopolar electrode (1-cm diameter disk) was used as a return for the monopolar DC electrode and was placed subcutaneously on the dorsum of the rat. The DC waveforms were delivered using a Keithley 6221 waveform generator (Keithley Instruments, Cleveland, OH, USA) controlled using a computer interface. A third cuff electrode was used for the delivery of HFAC during the combined HFAC and DC blocking experiments. This electrode was bipolar with a 1.0-mm edge-to-edge contact spacing and 1.0 mm of silicone between the edge of the outer platinum contact and each edge of the cuff [1, 4]. HFAC waveforms were 40 kHz voltage-controlled sinusoids and were delivered using a Wavetek 395 waveform generator (now Willtek Communications GmbH, Ismaning, Germany) controlled using a computer interface. A 40-kHz waveform was selected since the onset response tends to be reduced at higher waveform frequencies such as 40 kHz [8]. A few drops of medical saline were applied to the nerve preparation after electrode placement.

Preliminary experiments revealed that there was a significant leakage of the 40 kHz waveform through the DC cuff electrode back to the HFAC generator via the earth ground (despite the use of equipment with isolation). This leakage current resulted in strong activation of the nerve during delivery of HFAC (presumably at the site of the DC electrode). To minimize this leakage to a level which did not result in any activation of the nerve, a transformer (SP-49, Triad Magnetics, Corona, CA, USA) was used for connection of the HFAC generator to the HFAC electrode, and a 700-mH inductor was placed in series with the DC pathway. The connectivity of these two components is shown in Fig. 1.

2.2 Measurement of DC block thresholds

The minimum amplitude of DC required to block the nerve (the block threshold) was determined for each of 17 animals. For each trial, 1.5 Hz proximal stimulation pulses were delivered to the nerve through the proximal electrode, and a trapezoid-shaped ramped pulse of DC was delivered through the monopolar DC electrode. DC ramp waveforms consisted of either a 0.5 or 1.0 s ramp up from zero, a 1.0 s plateau, and a 0.5 or 1.0 s down ramp. The amplitude of the plateau was increased in successive trials until a complete conduction block was achieved as determined by a lack of muscle twitches during the plateau period. The block threshold was determined with a resolution of 300 μ A or less for most preparations. For preparations with a block threshold greater than 2.0 mA, the threshold was found with a resolution of 500 μ A. This coarse resolution was chosen to limit the number of DC deliveries to the nerve. Trials were performed approximately 1 min apart. Anodic currents were evaluated in 7 of the 17 rats, and cathodic currents were evaluated in each of the 17 rats. No reduction in proximally elicited muscle force was observed in any of these trials.

2.3 Measurement of nerve activation in response to DC ramps

The degree of nerve activation to various DC ramp times was measured using muscle force as an indicator in 6 of the 17 rats. In each experiment, seven trapezoid-shaped ramped pulses of DC were delivered through the monopolar DC electrode. Each trapezoidal pulse had a 0.5-s plateau period, and an up ramp and down ramp time that varied based upon a randomized assignment. Up ramp times of 0, 0.125, 0.25, 0.5, 1.0, 2.0, and 4.0 s were evaluated. Down ramp times of 0, 0.063, 0.125, 0.25, 0.5, 1.0, and 2.0 s were evaluated. All ramped DC waveforms for these trials were cathodic with a plateau amplitude equal to the DC block threshold. Trials were performed approximately 1 min apart.

2.4 Block of whole nerve using combined HFAC and DC

Each demonstration of conduction block using combined HFAC and DC consisted of three trials. The first trial consisted of HFAC to demonstrate that HFAC produced an onset response, the second trial used combined HFAC and DC currents to block the nerve without producing an onset muscle contraction, and the third trial was a repeat of the first with HFAC only to verify that the nerve still produced an onset response after DC delivery from the previous trial. All trials were performed approximately 1 min apart.

Typical waveform timing for a combined DC and HFAC block is shown conceptually in Fig. 2. Proximal stimulation was initiated at 1 Hz and continued for the duration of the trial. After 3–4 s, DC block was turned on using an amplitude ramp to reach a plateau that produced complete conduction block. Block was indicated by the absence of muscle twitches that would normally be produced by the 1 Hz proximal stimulation. Once the DC block reached a plateau, HFAC block was turned on at an amplitude of 150% of HFAC block threshold (as measured with 0.1 V resolution in a preceding trial [1, 3, 8]). An amplitude of 150% of block threshold was chosen since it typically resulted in an onset response that subsided within a few seconds. After a brief plateau, the DC block was then ramped down, leaving the HFAC block on. The trial was completed when the HFAC block

was turned off and the nerve resumed normal conduction, as evidenced by the return of the 1 Hz muscle twitches. For each of the animals, the experiment was terminated once signs of nerve damage appeared. This was done to prevent collection of data that pertained to an unhealthy preparation.

2.5 Nerve conduction failure with repeated DC delivery

A series of experiments were performed in five rats to investigate the effect of repeated DC delivery on acute nerve health. Our measure of acute nerve health was the nerve's ability to conduct action potentials through the site of the DC electrode as represented by peak evoked muscle twitch force. For these experiments, three electrodes were placed on the nerve: a bipolar stimulation electrode on the proximal sciatic nerve, a monopolar DC electrode, and a second bipolar stimulation electrode distal to the DC electrode. Both stimulation electrodes and the DC electrode were of identical design to those described in Sect. 2. Stimulation pulses were supramaximal for the motor efferents with a pulse width of 50 μ s and were delivered using a Grass S88. DC was delivered using a Keithley 6221.

For each experiment, 2-s unramped cathodic DC pulses were delivered to the nerve with an interpulse interval of 8-s (i.e., repeated every 10 s). The amplitude of the DC pulse was equal to the block threshold as measured in a previous trial. During the interpulse intervals, proximal stimulation and then distal stimulation were delivered at 1.5 and 2.5 Hz, respectively. The ratio of proximally evoked peak muscle force to distally evoked muscle force was used as a measure of the nerve's ability to conduct through the DC electrode site. This method ensured a measurement of conduction failure local to the center DC electrode, and accounts for any muscle fatigue that may occur during the experiment. Two different stimulation frequencies were used to ensure the differentiation of muscle twitches induced by each electrode. The timing scheme was chosen to allow for a reasonably small resolution for DC delivery (2.0 s) and to maintain enough time to deliver the proximal and distal stimulations.

The experiment was terminated once the proximal stimulation failed to produce a visible muscle twitch. The nerve was monitored periodically for at least 30 min post-DC delivery to test for a return of conduction.

3 Results

3.1 DC block thresholds

Complete cathodic DC conduction block, as measured by the absence of 1 Hz muscle twitches, was achieved in each of the 17 animals. For each of the seven animals in which anodic block was attempted, a partial conduction block was possible at intermediate currents, but strong nerve activation occurred during the plateau phase before complete block could be achieved at higher anodic currents as shown in Fig. 3a.

The degree of conduction block increased with increasing cathodic current amplitude as shown in Fig. 3b, and complete block was achieved with a mean amplitude of 1.63 mA and a standard deviation of 0.58 mA. No reduction in proximally elicited muscle force was observed during any of these trials.

3.2 Nerve activation in response to DC ramps

The degree of nerve activation to up and down ramps of various durations was evaluated in six animals. Two of those animals demonstrated a transient firing after the delivery of DC, which was associated with prolonged cumulative DC delivery (see Sect. 3.5). This transient firing confounded the measurement of field-induced nerve activation during the down ramp.

Therefore, the data from these two animals were not included in the analysis of ramp times; however, the up ramp activation levels for the two animals for which transient firing occurred demonstrated the same general trend as the other four animals for which it did not.

Figure 4a shows individual muscle force recordings from the first 500 ms of a trapezoidal DC pulse from a single representative experiment. The traces are organized in order of increasing ramp time from 0 to 4.0 s. The up arrows represent the timing of the start of the DC up ramp. All DC-induced muscle twitches were brief and occurred at the start of the DC ramp. Ramp times of 0 s resulted in a contraction that was slightly larger than a single maximal muscle twitch. The height of the twitch increased with a ramp time of 0.125 s and often increased again for a ramp time of 0.250 s. For ramp times larger than 0.250 s, nerve activation tended to decrease with increases in ramp time. For two of the animals, it was possible to achieve up ramps with zero activation for at least one of the ramp times tested. For two animals, there was some degree of activation for all ramp times. There was one notable exception to the trend of decreased muscle force with increased ramp time, where a 4.0 s ramp resulted in a substantial twitch despite an otherwise decreasing trend in twitch forces. This data point is shown in Fig. 4b (symbol 'x').

Figure 4b shows summary data for the peak force of the DC onset response with up ramp time in each of the four animals. The mean force of the DC onset response is shown with the solid circles connected by the bold line in this figure. These data show the general trend discussed above: an activation that was slightly larger than a twitch for 0 s, increasing activation for 0.125 and 0.250 s ramps and a decrease in activation for ramps of increasing length beyond 0.250 s.

Figure 5a shows individual muscle force recordings during the final 500 ms of a trapezoidal DC pulse for a single representative experiment. The traces are organized in order of increasing down ramp times from 0 to 2.0 s. The downward arrows represent the end of the DC down ramp. All of the DC-induced activations were brief and occurred at the end of the DC ramp. The 0-s ramp (step) resulted in a twitch that was similar in magnitude to a maximal muscle twitch. Increasing the down ramp time resulted in a decreased muscle twitch force.

Figure 5b shows summary data for the peak force of the DC break response with down ramp time in each of the four animals. The mean force of the DC down ramp response is shown with the solid circles connected by the bold line in this figure. These data show the general trend discussed above: a 0-s down ramp resulted in activation with a magnitude that was between one half and two times the peak force of a proximally elicited maximal muscle twitch, and muscle force decreased with increasing ramp time. Muscle activation was absent or negligible for ramp times of 0.5 s and greater in all animals.

3.3 Block of whole nerve using combined HFAC and DC

Partial or complete block of HFAC onset response was achieved in each of the six animals in which the combined HFAC and DC delivery was tested. As detailed in Table 1, complete block was achieved in four animals, and a minor onset response occurred in two of six animals due to insufficient DC amplitude. Figure 6 shows a sequence of three consecutive trials demonstrating block of the onset response with DC (the second combined block trial for animal number five). Each trial shows a recording of the muscle force and the timing of the HFAC waveform (indicated by the grey bar). The muscle force recording in Fig. 6a shows the onset response for a 40-kHz HFAC waveform. Figure 6b shows the combined use of HFAC and DC to block the transmission of the onset response. The timing of the DC is indicated by the dashed trace. Several seconds after the start of the trial the DC ramp was initiated, and resulted in an onset response (approximately 1.4 times the twitch force).

HFAC was delivered several seconds later, and the absence of the large onset response indicated that the DC blocked the onset firing induced by HFAC. The DC was ramped down to a zero current, and the block was maintained by HFAC. Figure 6c shows the following trial in which conduction block was achieved with HFAC only. This trial demonstrates that the DC did not eliminate the onset response simply by damaging the nerve, and that the block occurred as the result of a transient DC conduction block. Similar results were achieved in each of the six animals. Table 1 lists detailed results of these experiments.

3.4 DC-induced prolonged conduction failure

In most experiments, DC delivery induced a decrease in proximally elicited muscle force. This occurred in five of the six animals in which the combined HFAC and DC block experiments were performed (the animal which did not show signs of damage died before multiple combined block trials could be performed), and in each of the five animals in the repeated DC delivery series. Five of the six preparations in the combined block experiments exhibited a decrease in muscle force after only one combined HFAC and DC trial. Figure 6 shows trials from an animal in which there was no decrease in muscle force during a combined HFAC and DC trial. Figure 7 shows a combined HFAC and DC block trial which did result in a decrease in proximally elicited muscle force. Table 1 indicates the damage ratio after a single combined HFAC and DC trials for each of the six animals used for this type of experiment. The damage ratio is defined as $1 - (\text{post-DC twitch force} / \text{pre-DC twitch force})$, and reflects the relative decrease in proximally elicited muscle force after DC delivery.

Figure 8 shows the results of the repeated DC delivery experiments. Figure 8a summarizes how repeated DC delivery affected impulse transmission through the DC electrode region. The abscissa depicts the cumulative DC delivery time (in 2.0 s intervals), and the ordinate depicts normalized muscle force (proximally elicited force/distally elicited force). Each trace/symbol represents data from one of the five animals in which these experiments were performed. Each animal exhibited a sigmoidal decrease in normalized muscle force with cumulative DC delivery. The normalized muscle force declined to zero in each animal after sufficient DC delivery (<60 s of cumulative DC in each case) and did not recover within 30 min. There was no substantial decrease in the distally elicited muscle force during any experiment, indicating that the decrease in muscle force resulted from conduction failure, and that the portion of the nerve which failed to conduct was the site of the DC electrode.

3.5 DC-induced transient firing

In most experiments, multiple deliveries of DC to the nerve resulted in a transient muscle contraction after the cessation of the DC pulse. This occurred in two of six animals in the DC ramp series, in four of six animals in the combined block series, and in each of the five animals in the repeated DC delivery series. An example of this transient firing is indicated in Fig. 7 by the large outlined arrow.

This firing was most closely studied in the repeated DC experiments. Figure 8b summarizes the DC-induced transient firing which occurred in this series of experiments. The abscissa depicts the cumulative DC delivery time (in 2.0 s intervals), and the ordinate depicts the peak value of the post-DC force (transient firing) normalized to a distally elicited muscle twitch. The matching symbols of Fig. 8a, b correspond to the same animals. The DC pulses which were delivered in this series of experiments were not ramped, so these data are confounded by anodic break contraction. However, these data show an increase in post-DC contraction force with cumulative DC (with the exception of the animal with symbol '◆', for which a large contraction occurred after each 2.0 s DC pulse).

The amplitude of DC flowing from the monopolar cuff electrode was monitored using a series 100 Ω resistor in each trial of each experiment. The voltage measurement across this resistor indicated that a ~10 ms anodic current spike with an amplitude approximately equal to one half of the blocking amplitude sometimes occurred at the end of the DC pulse during the repeated DC delivery experiments. No spurious current flow occurred during any of the DC ramp trials. These measurements suggest that the transient firing (which typically lasted 3 s) was not induced by currents flowing from the DC electrode.

4 Discussion

This study demonstrated that it was possible to block the onset response generated by HFAC using cathodic DC delivered through a separate blocking electrode in each of the six animals tested. In all cases, the ramped DC waveform produced an onset response that was substantially smaller than that produced by HFAC, or did not produce an onset response at all. This suggests that the combined conduction block produces a favorable onset response relative to HFAC block alone.

The DC ramp experiments performed in this study demonstrated that in some animals it was possible to completely eliminate the DC onset response using a sufficiently long up ramp (at least 1.0 s in this study). However, in some animals even a 4-s up ramp was not sufficient to eliminate the onset response. These experiments also demonstrated that it is possible to completely eliminate the nerve activation that occurs directly following a DC pulse using a sufficiently long down ramp (0.5 s or longer). These results are consistent with previous studies that showed successful DC block without onset firing using similar techniques [31, 43], and a study by Zimmerman that showed that 3.0 s ramps were not sufficient to eliminate activation in some cases [43]. A 0 s up ramp was found to produce a muscle activation that was equal to or only slightly larger than a proximally elicited muscle twitch in all cases. Intermediate ramps of 0.125–0.250 s produced the worst onset firing. This non-monotonic relationship between nerve activation and ramp time is novel to this study. A future simulation study could help to elucidate the nature of this non-monotonic relationship. Given that a typical HFAC onset response has a magnitude that is typically three to five times that of a maximal muscle twitch [2, 8] and can last for several seconds (in contrast to the brief onset response which occurs with a DC ramp as shown in Fig. 4), either ramped or non-ramped DC block may be attractive methods of blocking HFAC onset response with reduced or negligible nerve firing.

When activation occurred during DC ramps, it always occurred at the beginning or at the end of the ramp for up ramps and down ramps, respectively. This is consistent with other published results [31, 43] and suggests that the lowest threshold motor fibers (large diameter, close to the electrode) are responsible for the activation. This same conclusion was reached by Hennings [20] who published a study of ramped waveforms to selectively block large diameter fibers and activate those with a small diameter. This would suggest that an exponential ramp shape could be much more efficient at minimizing DC activation and should be evaluated in the future.

Only cathodic currents were found to be capable of producing a complete conduction block in this study. Complete anodic block could not be achieved, and nerve activation occurred at higher anodic current amplitudes. Bhadra and Kilgore [7] have suggested that three types of DC conduction block are possible: true cathodic block (caused by depolarization of axons beneath a cathodic electrode), virtual anodic block (caused by hyperpolarization of axons by a virtual anode site adjacent to a cathodic electrode), and virtual cathodic block (caused by depolarization of axons by a virtual cathode site adjacent to an anodic electrode). Cathodic block results from the depolarization-induced inactivation of sodium channels, and anodic

block results from a membrane hyperpolarization that is sufficient to prevent a fiber from reaching threshold when an action potential arrives at the block site. The complete motor conduction block achieved in this study was likely achieved by a combination of true cathodic block and virtual anodic block. True cathodic block likely occurred for the high threshold motor fibers (small axon diameter and distant from the electrode), and virtual anodic block likely occurred for the low threshold motor fibers (large axon diameter and near to the electrode) due to the high field intensity they experienced [7]. The anodic break excitation shown in Fig. 5a, b is evidence that at least a portion of the fibers experienced the significant hyperpolarization associated with virtual anodic block.

Complete block of the onset response was not achieved in some of the preparations. This was likely the result of an underestimate of the DC block threshold during the threshold finding procedure. It seems likely that the DC field was not sufficient to block a small population of the sciatic motor neurons during the threshold finding procedure (perhaps even just one or two motor units given that there was no observable twitch). We postulate that the proximally elicited muscle twitch was sufficiently small that it went unnoticed during the threshold finding procedure, but the larger HFAC-induced twitch resulting from multiple action potentials during the onset response was more noticeable. This is consistent with the N-let summation of action potentials observed by Karu et al. [22] when multiple stimuli were delivered in rapid succession. This observation suggests that using N-let style proximal stimulation may be a more sensitive stimulus type for finding conduction block thresholds.

This study characterized a decrease in muscle force that occurred with DC delivery. We postulate that the decrease in muscle force was due to damage to individual axons that was sufficient to prevent them from conducting action potentials. This is consistent with a reduction in compound action potential magnitude which has been published previously by Whitwam and Kidd [40]. Interestingly, in the repeated DC delivery experiments, a decline in muscle force did not occur for cumulative DC delivery times of <12.0 s, whereas a decline in muscle force occurred with as little as 6.5 s of DC delivery (plateau plus ramps) in the combined block experiments. Damage also did not occur for the threshold experiments. This could be the result of using shorter DC pulses in the repeated delivery and threshold experiments (2.0 and ~1.0 s, respectively) than for the continuous DC delivery time (6.5 s) used for the combined block experiments. This suggests that the damaging effects of DC delivery are likely not simply additive. This disparity could also potentially be the result of an unknown interaction between HFAC and DC currents.

In each of the experiments in which the nerve exhibited a decrease in muscle force, a transient activation of the nerve was also evident in the form of a large muscle contraction following the DC pulse. The results of these experiments do not reveal the exact origin of this contraction; however, we postulate that it may be an indication of nerve damage. It is well established that long pulses of DC exhaust the safe chemical mechanisms of charge delivery for platinum electrodes, resulting in the reduction of water and the generation of reactive oxygen species [29]. Reactive oxygen species are known to damage cell membranes, myelin, and protein and may contribute to the transient firing seen in this study by allowing abnormal ion flow across the cell membrane [6]. Monitoring of the amplitude of the DC flowing from the DC electrode (using a series 100 Ω resistor) demonstrated that there was no current flowing through the DC electrode during the period of contraction, suggesting that the contraction did not result from spurious leakage or discharge currents. This transient contraction is an important issue to be resolved since the utility of the combined blocking technique lies in the induction of conduction block without current-induced contractions.

This study has shown that the combined use of direct and HFAC can be used to successfully produce a conduction block in which onset response firing is not transmitted to the end organ. This indicates, for the first time, a particular strategy to approach the problem of the onset response in HFAC: using a separate, brief block to stop the HFAC onset response from propagating. In this article, we have established the general characteristics under which DC block can be accomplished without producing an onset activation of its own (or sometimes producing a non-zero response which is less in magnitude than the HFAC response). It will now be necessary to investigate mechanisms of safely delivering DC to a nerve. This could be achieved through some combination of the following five mechanisms, or others. First, the duration of required DC delivery could be reduced by shortening the duration of the HFAC onset response. This could be achieved by utilizing a higher blocking waveform frequency (frequencies as low as 3 kHz can be used to produce conduction block, however induce longer periods of onset firing) [8] or amplitude [8], or by using a narrower bipolar cuff electrode [2]. Second, the total amount of DC charge injection required for block could be reduced. This could be achieved through the utilization of non-linear DC ramps, or possibly through alternative DC electrode configurations, e.g., bipolar, which could be used to focus the applied field. For example, exponentially decaying waveforms have successfully been used to reduce activation during a down ramp with minimal charge delivery and require less DC charge injection than linear ramps [12, 39, 43]. Third, the material and design of the DC electrode could be chosen to maximize safe charge transfer. For example, Petruska et al. [31] have delivered DC using a silver–silver chloride electrode and do not report adverse effects. Iridium oxide [5] or tantalum [18] are appropriate for chronic implantation and are also potential candidate materials. Finally, a safer alternative net-DC waveform could be used. For example, ElBasiouny and Mushahwar [14] have shown in a simulation study that axonal conduction can be reduced through the delivery of subthreshold imbalanced biphasic pulses. This type of waveform has been shown to have a higher damage threshold than equivalent DC stimulation [35]. A clinical blocking system may also incorporate a second proximally placed DC blocking electrode to block the proximally traveling onset response.

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Fig. 1. Schematic representation of the HFAC + DC setup. The 100-Ω resistor was used to monitor DC current flow. The isolation transformer and inductor were used to squelch HFAC leakage

Fig. 2.
Example timing of proximal stimulation, DC, and high frequency currents for the combined DC and HFAC experiments

Fig. 3. Response of the nerve to ramped **a** anodic and **b** cathodic DC waveforms of various amplitudes

Fig. 4.
a Individual muscle force recordings from the first 500 ms of a trapezoidal DC pulse from a single experiment. *Up arrows* demarcate the ramp start time for each trace. **b** Peak force measurements of DC onset response to each of the up ramp times tested for four animals. *Each symbol* represents data from an individual animal. The mean is shown with *filled circles* connected by a *bold line*

Fig. 5.

a Individual muscle force recordings from the final 500 ms of a trapezoidal DC pulse from a single experiment. *Down arrows* demarcate the ramp end time for each trace. **b** Peak force measurements of DC onset response to each of the down ramp times tested for four animals. *Each symbol* represents data from an individual animal. The mean is shown with *filled circles* connected by a *bold line*

Fig. 6. Sequence of three consecutive trials demonstrating block of the onset response with DC. Each trial shows a recording of the muscle force and the timing of the HFAC waveform (indicated by the *grey bar*). **a** Muscle response to a 40 kHz HFAC waveform. **b** Muscle response to combined delivery of HFAC and ramped DC. The timing of the DC is indicated by the *dashed trace*. **c** Muscle response to a 40 kHz HFAC waveform

Fig. 7. Combined HFAC and DC block trial with signs of nerve damage. *Outlined arrow* indicates a large transient muscle contraction that occurred immediately following the cessation of the DC delivery. The immediate decrease in the muscle force elicited by proximal stimulation is also indicated

Fig. 8.

a Results of repeated DC delivery experiments show a decline in proximally elicited muscle force, indicating nerve conduction failure with cumulative DC delivery. Proximally elicited muscle force was normalized to distally elicited muscle force. **b** Results of repeated DC delivery experiments show an increase in post-DC contraction force with cumulative DC delivery. Muscle force was normalized to that of a distally elicited twitch

Table 1

Relevant experimental measurements from the combined block series of experiments

Animal number	DC amplitude (mA)	Up ramp time (s)	Plateau time (s)	Down ramp time (s)	DC ramp response: up/down	HFAC onset response without DC	HFAC onset response with DC	Damage ratio: 1 – (post-DC force/pre-DC force)
1	3.0	4.0	3.0	1.0	0.11 X	2.68	0.18	0.16
2	1.9	2.0	3.5	1.0	0.0 0.0	2.56	0.0	0.0
3	2.5	0.0	7.5	0.0	1.0 X	3.32	0.0	0.57
4	2.5	0.0	6.5	0.0	0.06 X	3.71	0.0	0.33
5	1.0	4.0	4.5	0.25	0.0 0.0	2.65	0.02	0.02
6	2.5	0.0	5.5	1.0	0.62 X	2.51	0.0	0.03

Columns 2–5 describe the parameters for the DC waveform. Columns 6–8 describe the peak force of the muscle twitch induced by DC and HFAC waveform delivery (the peak force is normalized to the preceding proximally elicited twitch force in the trial). Column 9 describes the ratio of the muscle force before and after DC delivery to indicate any lasting conduction failure in the nerve