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Combined KHFAC+DC nerve block without onset or reduced nerve conductivity after block

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Abstract

Background—Kilohertz Frequency Alternating Current waveforms (KHFAC) have been shown to provide peripheral nerve conductivity block in many acute and chronic animal models. KHFAC nerve block could be used to address multiple disorders caused by neural over-activity, including blocking pain and spasticity. However, one drawback of KHFAC block is a transient activation of nerve fibers during the initiation of the nerve block, called the onset response. The objective of this study is to evaluate the feasibility of using charge balanced direct current (CBDC) waveforms to temporarily block motor nerve conductivity distally to the KHFAC electrodes to mitigate the block onset-response.

Methods—A total of eight animals were used in this study. A set of four animals were used to assess feasibility and reproducibility of a combined KHFAC+CBDC block. A following randomized study, conducted on a second set of four animals, compared the onset response resulting from KHFAC alone and combined KHFAC+CBDC waveforms. To quantify the onset, peak forces and the force-time integral were measured during KHFAC block initiation. Nerve conductivity was monitored throughout the study by comparing muscle twitch forces evoked by supra-maximal stimulation proximal and distal to the block electrodes. Each animal of the randomized study received at least 300 seconds (range: 318 to 1563s) of cumulative DC to investigate the impact of combined KHFAC+CBDC on nerve viability.

Results—The peak onset force was reduced significantly from 20.73 N (range: 18.6–26.5 N) with KHFAC alone to 0.45 N (range: 0.2–0.7 N) with the combined CBDC and KHFAC block waveform ($p<0.001$). The area under the force curve was reduced from 6.8 Ns (range: 3.5–21.9

Ns) to 0.54 Ns (range: 0.18–0.86Ns) ($p < 0.01$). No change in nerve conductivity was observed after application of the combined KHFAC+CBDC block relative to KHFAC waveforms.

Conclusion—The distal application of CBDC can significantly reduce or even completely prevent the KHFAC onset response without a change in nerve conductivity.

Keywords

Kilohertz High Frequency Alternating Current; Nerve Block; Onset response; HFAC; KHFAC; Direct Current; charge balanced DC; CBDC

Introduction

Electrical nerve conduction block can provide a controlled interruption of motor and sensory nerve activity [1–4]. Potential applications of motor block include the reduction of spasticity in movement disorders, such as blocking urethral sphincter spasms for bladder control following spinal cord injury or localized muscle spasms after stroke or dystonia [5, 6]. Potential applications of sensory nerve block include reduction of chronic pain [4] and modulation of autonomic activity by blocking activity in sympathetic or parasympathetic fibers [1]. Kilohertz-frequency alternating current (KHFAC) waveforms can provide this form of electric nerve block on demand, but cause an undesirable transient burst of action potentials upon initiation of the block waveform (the “onset response” [7]). This onset response can lead to intense muscle contractions (see Fig. 1 A) and pain, limiting clinical applications of this technology. Various attempts have been made to eliminate the onset response, including electrode modifications [8], optimizing KHFAC waveform parameters [7,8], and adding other forms of nerve block such as cooling [9] or direct current [10]. However, these techniques are either impractical for clinical implementation or do not completely suppress the onset response [7, 9, 11, 12]. Direct current (DC) waveforms, in contrast to KHFAC, can achieve an electric nerve block *without* an onset response (Fig. 1 B) [13]. This is accomplished by gradually ramping the amplitude of the DC waveform until a full nerve conduction block is achieved, a technique that was investigated for KHFAC waveforms as well, but without success [11, 14]. However, the disadvantage of DC nerve block is that unidirectional charge injection into the electrode-electrolyte interface could cause irreversible faradaic reactions [15, 16]. These reactions could cause the dissolution of the electrode, generation of charged free radicals or platinum salts, or the evolution of gaseous hydrogen or oxygen [17]. The byproducts of the faradic reactions can affect neural conductivity after block over short durations and nerve damage when applied for longer periods [10, 13, 17, 18]. Separating such interfacial processes from the DC charge delivery electrode may be able to maintain neural excitability [19].

In this study, we tested the feasibility of using a charge balanced direct current (CBDC) waveform that incorporates a first (e.g. cathodic) phase to provide DC nerve block and a secondary (e.g. anodic) phase to achieve charge balance. The conceptual basis for the CBDC block is that the charge delivered during the block phase is stored in the double-layer capacitance of the electrode-electrolyte-interface. If the injected charge is limited to less than the maximum that can be stored in the double-layer, all the current injected in the several seconds of the nerve block phase would be recovered over the duration of the charge

balancing phase. Two studies by Vrabec et al., showed proof of this concept by using a high surface area platinum-black (platinized platinum) electrode [20, 21], demonstrating that the CBDC waveform can provide a short-term (tens of seconds) nerve block without causing permanent changes in nerve conductivity following block [21]. In a study by Vrabec et al., potentials measured between the block electrode and an Ag/AgCl reference electrode during the application of the CBDC-block did not reach or exceed the limits of the water window [21][15]. As a result, the study authors concluded that oxygen evolution and hydrogen evolution did not occur at the DC block electrode. Typical Pt-black electrodes of 3 to 9 mm² active surface area were fabricated with charge injection capacities of tens of milli-coulombs. In order to produce DC nerve block, cathodic current in the range of 1 to 2 mA was applied. Using these values, the DC could be delivered for tens of seconds while maintaining the total charge within 90% of the water window [20] [16]. Complete DC nerve block was achieved with this approach and the onset response that can result from the initiation of the CBDC was avoided by slowly ramping the DC to the blocking value [22]. Unfortunately, because of the necessity for a recharge phase to balance the charge injected during the nerve block phase, the CBDC nerve block alone did not allow for a continuous nerve block beyond tens of seconds.

Ackermann et al. demonstrated that it is possible to block the motor onset response with the use of a second platinum electrode, distal to the KHFAC block electrode, delivering a brief DC block [10]. However, after only a few repetitions, the DC electrode caused a permanent reduction in the conductivity of the nerve. The use of high charge capacity electrodes in combination with the CBDC waveform allow for a longer DC delivery without causing a reduction in the conductivity of the nerve. Using this approach, we hypothesized that the CBDC waveforms could provide a nerve conduction block for a duration long enough to block the KHFAC onset response. Thus, by combining KHFAC and CBDC nerve block, it should be possible to produce a nerve conduction block without an onset-response that could be maintained for hours (using the KHFAC block alone) and still allow reversibility of the block when the waveform was stopped. The objective of this study was to explore the feasibility of using this combined KHFAC+CBDC approach to provide a nerve block that minimizes the onset response and can be maintained for long periods of time without affecting nerve conductivity after block. We specifically wanted to address the following questions: (1) to what extent can the onset-response be reduced with the combined block waveform? (2) How stable is the block? (3) Does the application of the combined block waveform have an effect on nerve conductivity following hundreds of seconds of cumulative DC delivery? (4) Could the secondary recharge phase cause a break or reversal of the block, e.g. due to crosstalk between the two different waveforms?

Methods

The study was conducted on a total of eight adult Sprague-Dawley rats. An initial feasibility study, conducted on four of the animals, was used to assess whether a combined KHFAC + CBDC nerve block could be achieved repeatedly and allowed the optimization of the electronic setup. Based on a power analysis ($\alpha=0.05$) using the data acquired during the initial feasibility study, a sample size of four was required to demonstrate a significant reduction of the KHFAC-induced onset response and to demonstrate that nerve conductivity

was retained after block was stopped. All procedures were conducted following prior approval by the institutional animal care and use committee at Case Western Reserve University, Cleveland, Ohio, USA.

Surgery

The surgical procedure has been described in detail previously [10, 23, 24]. Briefly, the animals were anesthetized with intra-peritoneal injections of Nembutal (phenobarbital sodium). One of the hind legs was shaved and an incision made along the lateral aspect of the leg and thigh. The biceps femoris was reflected, and the sciatic nerve exposed from 1 cm lateral to the spine to its distal branching into the tibial and common peroneal nerves. The tibial nerve was exposed to its branches to the gastrocnemius muscle. The sural and common peroneal nerves were crushed using a hemostat to prevent motion artifacts from the tibialis anterior muscle. The gastrocnemius-soleus muscle complex was dissected, and the calcaneal (Achilles) tendon severed from its distal attachment. The tibia was fixed to the table using a clamp, and the calcaneal tendon attached to a force transducer (Entran, Fairfield, NJ; resolution 0.005 N) with 1–2 Newtons of passive tension.

Electrodes

Four electrodes were placed on the sciatic nerve, two each for stimulation and block (Fig. 2). The proximal (PS) and distal (DS) stimulation, as well as the KHFAC waveforms, (Fig. 3) were delivered using bipolar platinum J-cuff electrodes as described in Foldes et al. [25]. The CBDC block was applied using a monopolar electrode of high charge injection capacity with a return path through a needle electrode, placed sub-cutaneously in the animal's back. The CBDC block electrode was manufactured by electrochemical platinum deposition on a platinum foil substrate (Pt-black) of 3 X 3 mm² surface area. The charge injection capacities of the electrodes used for the experiments were 27mC, 41 mC, 21 mC and 20 mC for animals 1–4, respectively. The charge injection capacities were measured prior to the experiments as described in Vrabec et al. [26, 27], and were high enough to allow CBDC-block for up to a few tens of seconds [22]. The PS electrode was positioned on the most proximally exposed part of the nerve, and the DS electrode close to the gastrocnemius muscle. Both of the block electrodes were placed in between the PS and DS electrodes, with the KHFAC electrode proximal to the CBDC electrode.

Electrical Waveforms

A Grass S88 stimulator (Grass Technologies, West Warwick, RI) was used to deliver PS at 2 Hz and, on a second isolated channel, DS at 1 Hz (Fig. 3). Both the PS and DS waveforms were current-controlled, 20μs long pulses that caused supramaximal twitches. The KHFAC block waveform was a charge-balanced, voltage controlled, sinusoidal, 20 kHz signal generated by a waveform generator (Wavetech 395, Fluke, Everett, WA). A DC filter circuit [28] was placed between the KHFAC generator and electrode to prevent the accumulation of unintended DC charges in the electrode-electrolyte interface (Fig. 2). This DC filter circuit consisted of two capacitors of 1 μF each (in series with the electrode) and two inductors of 8.2 H each (in parallel with the electrode). The amplitude of the KHFAC waveform was chosen to be about 125% of the block threshold in order to achieve KHFAC-only onset response durations of five seconds or less [29].

The current-controlled, cathodic block waveform for CBDC block was provided by a custom-built, battery-powered, voltage-to-current converter (DC-offset $<1\mu\text{A}$) that received a voltage-controlled signal from a USB DAQ-6258 (National Instruments, Austin, TX). This voltage-controlled signal was designed before each trial on a custom-built program (Labview, Austin, TX), allowing independent customization of the shape of the cathodic block phase and the anodic charge-balancing phase. Both phases of the signal had adjustable on- and off-ramps with durations of up to several seconds in order to achieve the DC-block without nerve activity caused by the block onset or an anodic break at the end [13]. In some cases, an extra inflection point was used in the middle of a ramp (Fig. 4, Fig. 5) to achieve a full DC block without generating an onset response. The amplitude of the plateau of the cathodic phase of the DC block was chosen as the current sufficient to reduce the maximum KHFAC onset-response force to levels below the forces evoked by PS. Once this amplitude had been reached at the end of the DC ramp, it was held constant as a plateau current for 2–10s in order to block the KHFAC onset activity. The CBDC waveform timing parameters were chosen to ensure that the net charge injected into the electrode-electrolyte interface was less than 90% of the charge injection capacity of the DC block electrode. Once the cathodic block had been successfully established, the anodic amplitude of the recharge phase was chosen to be 10% of the cathodic plateau current (or a maximum of 0.2 mA) to avoid anodic activation of the nerve. This low current level in combination with on- and off-ramp durations of 2 to 8 seconds ensured the absence of new stimulation effects during the recharge phase, caused by either virtual cathodes, anodic break or crosstalk from the KHFAC waveform. The charge injected during the anodic phase was set to 100% of the charge injected during the cathodic phase. A combination of voltage-controlled KHFAC and current-controlled CBDC block was chosen because it resulted in the least crosstalk between the electronic waveform generator circuits during the initial feasibility studies.

The maximum duration of the cathodic DC block phase was limited by the charge-injection capacity of the electrode, and the current needed to achieve a successful mitigation of the KHFAC onset response. We attempted to minimize the DC block duration to (1) shorten the DC recharge time (which could exceed 100 seconds, taking up the majority of the block trials duration), and to (2) remain as far from the maximum injectable DC charge limit ($\leq 90\%$ of max). We further minimized the required duration of the cathodic DC phase by selecting KHFAC block parameters (frequency, amplitude, electrode contact spacing etc.) such that the onset-response would be no more than five seconds long. In vitro experiments with our Pt-black electrodes show a reduction in charge capacity over the duration of an experiment. This may be the result of poor mechanical properties of Pt-black electrodes.

Data acquisition, reduction and analysis

All data were sampled at 1 kHz using a custom designed software interface running a data acquisition card (NI6258, National Instruments, Austin, TX) [10, 23, 30]. Three waveforms were acquired: (1) the force due to the contraction of the gastrocnemius muscle evoked by electrical stimulation, and the voltage signals corresponding to the (2) KHFAC and (3) DC block waveforms.

Activation and saturation thresholds for the PS and DS electrodes were acquired at the beginning of the experiment and verified every half hour to ensure complete activation of the nerve. Since both stimulating electrodes fully activated the nerve, any difference between forces resulting from PS and DS activation are related to nerve conduction through the region of the nerve between the two electrodes (directly under the blocking electrodes) [2]. Thus, the ratio of the peak force generated by proximal stimulation to the peak force generated by distal stimulation (“PS/DS-ratio”) provides one method to assess acute changes in nerve viability for the duration of the experiment. Recording the PS/DS-ratio at the end of every trial provided a record of nerve viability over time.

Block thresholds were determined individually for the CBDC and KHFAC waveforms using suppression of twitches evoked by PS as the measure of block outcome. The optimal parameters for the combined KHFAC+CBDC block waveform were determined as follows: the CBDC block was first initiated with a slow ramp to prevent onset activity, then the slope of the ramp was increased to reach the CBDC block plateau (DC block threshold) as quickly as possible without causing an onset response. The DC block plateau was maintained for at least 0.5 seconds prior to the initiation of the KHFAC waveform to ensure that DC block was fully established. The KHFAC waveform was initiated at the previously determined threshold amplitude (no amplitude ramp was used with the KHFAC). If the CBDC block reduced the peak force of the onset response from the KHFAC so that it was less than the twitch force from proximal stimulation, the trial was considered successful. To determine the optimal CBDC-block plateau amplitude, the value was then increased in subsequent trials, until the peak-onset force could not be distinguished from noise, or until the charge injection capacity of the DC electrode was reached.

Each group of trials consisted of five combined KHFAC+CBDC trials and one KHFAC-only trial. Within each group, the trials were randomized in a pre-determined order that was different for each animal. The order in which KHFAC and the KHFAC+CBDC waveforms were applied was randomized, providing a unique sequence set for each animal. If the health of the animal deteriorated, requiring an early termination, a ratio of three combined block trials to one KHFAC trial was performed. The ratio of five to one was chosen as an optimum between maximizing the number of combined block trials, while collecting sufficient KHFAC trials, within the time available (experiment duration per animal: 5.5, 6.5, 6, and 8.5 hrs). The end-of-experiment criteria for the first three animals was the acquisition of at least six KHFAC only (control) and 20 combined block (KHFAC+CBDC) trials, while having applied the CBDC waveform for at least 300 seconds of cumulative DC delivery time during the KHFAC+DC block trials. We chose the value of 300 seconds because the PS/DS ratio in the majority of the animals tested by Ackermann et al. had dropped to 50% after 30 seconds of cumulative *unbalanced* DC, indicating acute nerve damage [10]. Thus, 300 seconds represented a 10-fold increase in charge injection.

Data reduction was done offline using custom-written Matlab routines. For each application of the block waveform the following data were computed: peak twitch force both before and after block application with PS and DS stimulation; peak force and area under the onset response curve; ratio of twitch force evoked by PS and DS (PS/DS); cumulative time of cathodic DC delivery; and the total charge delivered. Statistical analysis was performed

using JMP (SAS, Cary, NC). Normality of data was verified using the Kolmogorov-Smirnov test. Since the measures of onset response were not normally distributed, the Mann-Whitney U test ($U(\text{DoF})$), was used to assess the effect of block type and animal on peak force and area under the force-time curve during the onset response. Bonferroni correction of the p value was used to avoid an increase in type I errors due to the multiple comparisons. Additionally, a paired t-test was used to compare the onset response during the combined block trials to the average twitch force evoked by PS forces recorded in the same trial prior to block.

To assess the effects of repeated DC stimulation on nerve conductivity, a regression model was built with animal, trial number, cumulative charge injected and cumulative time of DC application as predictor variables; the PS/DS ratios during the combined-block trials were determined to be normally distributed and hence, the least squares regression method was used. The following statistics are reported for the model in the results section: the total variance in the data explained by the model (R^2), the F statistic and associated p value for the model, the coefficient estimate for each predictor variable and the corresponding p value. The two sample t test ($t(\text{DoF})$) was used to compare the PS/DS ratio during the KHFAC and combined block trials.

Results

Nerve conduction block was successfully achieved in all four animals, as well as the four animals testing in the feasibility group. Specifically, 100% of the motor twitch response could be eliminated using KHFAC alone, CBDC alone, and KHFAC+CBDC methods. The combined KHFAC+CBDC block reduced the onset response resulting from the KHFAC block alone in all four animals (Fig. 6 and Fig. 7) and in all four animals in the feasibility group. Neither the application of CBDC nor the combination of CBDC and KHFAC waveform caused a reduction in nerve conductivity beyond the termination of waveform delivery (Fig. 8).

The onset response was reduced with the combined block waveform

The choice of block type had a significant effect on peak-onset force (Mann-Whitney $U(1)=10.8$; $p<0.0001$) and the area under the curve ($U(1)=10.6$; $p<0.0001$) (Fig. 6). Peak-onset force reduced from 20.73 N (range: 18.6–26.5 N) with KHFAC alone to 0.45 N (range: 0.2–0.7 N) with combined CBDC and KHFAC, from 6.8 N (range: 3.5–21.9 N) with KHFAC alone to 0.54 N (range: 0.18–0.86N) with combined CBDC and KHFAC, and the mean area under the curve reduced from 6.8 Ns (range: 3.5–21.9 Ns) to 0.54 Ns (range: 0.18–0.86Ns) (Fig 6). Both the peak-onset force ($U(3)=17.1$; $p=0.0007$) and the area under the curve ($U(3)=19.5$; $p=0.0002$) varied between the animals as well.

The peak-onset force during the combined-block trials was significantly smaller than the peak muscle twitch force resulting from supramaximal sciatic nerve activation (5.1 ± 1.0 N vs. 0.7 ± 1.1 N; $t(163)=49.8$; $p<0.0001$; Fig. 6 far right), as was the area under the force curve (0.6 ± 0.4 Ns vs. 0.2 ± 0.1 Ns; $t(163)=-10.6$; $p<0.0001$; Fig. 7 far right). The CBDC and KHFAC amplitudes were consistent throughout the experimental session, and produced reproducible and stable reduction of the onset response. Furthermore, we were able to

achieve a complete reduction of the onset force in all animals using the combined CBDC +KHFAC nerve block.

Application of the block waveforms did not affect nerve conductivity

The PS/DS-ratio was not statistically different between the combined (0.99 ± 0.03) and the KHFAC (0.99 ± 0.04) nerve block ($t(1) = -0.52$; $p = 0.6$). Across all animals, the coefficient of variation for the PS/DS ratios was approximately 3%. Regression analysis indicated that the four predictors explained 53% of the variance ($R^2 = 0.53$, $F(6,157) = 29.6$, $p < 0.0001$). It was found that only the animal variable ($\beta_1 = 0.027$, $\beta_2 = 0.017$, $\beta_3 = 0.03$ and $\beta_4 = 0.01$, $p < 0.0001$) significantly contributed to the variability in the PS/DS ratio, whereas trial number ($\beta = 0.0004$, $p < 0.74$), cumulative DC charge ($\beta = 0.0002$, $p < 0.14$) and time ($\beta = 0.000$, $p < 0.06$) did not. The average cathodic DC plateau time without ramps was 2.5 ± 1.5 s (range 1 to 7 s, median 2.6 s). The overall average cathodic DC delivery time (Table 2), including ramps, was 16.5 ± 9.7 s (range 6 to 33.3 s, median 11.5 s). The injected charge during cathodic DC block for all combined block trials was 11.5 ± 2.5 mC (range 6.4 to 18.8 mC, median 11.3 mC, $n = 163$, $N = 4$).

Stability of block parameters

The CBDC average plateau amplitude during the combined waveform block trials was 2.3 ± 0.4 mA ($n = 164$). The average KHFAC amplitude, used for both the KHFAC-only and the combined KHFAC+CBDC trials, was 6.8 ± 1.6 V ($n = 211$). The average parameters across all successful combined block trials for each animal can be found in Table 1. The optimal parameters, found after an average of twelve initial trials per animal, are listed in Table 2.

Optimal waveform parameters

The primary differences between the parameters for each animal were the ramp and plateau durations for the CBDC block. In order to prevent an onset during the initiation of the CBDC block for animals three and four, the cathodic ramp required an additional inflection point (Table 3). This provided a ramp with two slopes: an initial shallow slope to reach a current value of -0.8 mA (animal 3) and -0.4 mA (animal 4), and a steeper slope to reach the cathodic CBDC block plateau. In addition, animal 4, required a two segment off-ramp of the cathodic phase to prevent neural firing during as the CBDC waveform was transitioned to the recharge (anodic) phase (Table 3).

Reduction in charge injection capacity

We observed a reduction in the charge injection capacity in every animal of the randomized study: the value of the electrode used in animal 1 changed from 27 mC before the experiment to 3.7 mC after the experiment. The reduction in animal 2 was less severe, from 41 mC to 36 mC; the value for animal 3 post-experiment is unknown as the electrode broke during or immediately after explantation, before it could be cleaned. The change observed in animal 4 was from 20 mC prior to 3 mC at the end of the experiment.

Discussion

This study demonstrated the feasibility of an electrical nerve block that combines the advantageous features of KHFAC and CBDC waveforms. We were able to initiate a combined KHFAC+CBDC nerve block in eight animals without an onset response and demonstrated, in four animals, that a statistically significant reduction of the onset force and area can be achieved. Once initiated, the electrical nerve block can be maintained for tens of minutes without a reduction in nerve conductivity after termination of the electrical block. For the purposes of many clinical applications, a complete reduction of the KHFAC onset response is desirable, and this goal was achieved in every animal once proper block parameters were found. A reduction of the onset peak force to levels below a muscle twitch marked a major improvement in comparison to the normal forces measured during KHFAC block onset response. In comparison, muscle twitch stimulation is routinely performed in the clinic to measure nerve conductivity and is well tolerated. Thus, a combined nerve block approach could provide a means to translating nerve block technology from bench to bedside, providing a tool in addition to neuro-stimulation to interface with the nervous system and modulate activity for better patient benefit.

We used an approach similar to Ackermann et al. [10], who attempted to reduce or completely eliminate the KHFAC onset response with a distally applied, *conventional* DC block. The main differences between the approach used in this study and the one tested by Ackermann et al are: the charge balanced DC waveform, the Pt-black electrode of high charge injection capacity used to provide the CBDC block, and the use of an inductor circuit to limit unintentional DC contamination of the KHFAC waveform and to prevent crosstalk between the KHFAC and DC-electrode [28]. The combination of the CBDC waveform and the Pt-black electrode, although limited to delivery of block for a few tens of seconds at a time, did allow flexibility in the design of the CBDC waveform. In some cases, it was necessary for the CBDC current ramp to exceed 20 seconds in order to avoid the generating unwanted neural activity. In order to block the onset response, the ramped reduction of the cathodic block phase was chosen to be longer than the onset response. If the CBDC block duration was too short, and the KHFAC onset response had not ended, we observed a transient muscle contraction of approximately twitch force amplitude that began as the cathodic phase of the CBDC block was being decreased to zero. The transient forces could be eliminated by increasing the CBDC block plateau or ramp duration by a few (2–5) seconds. We did not note a reduction in the forces evoked by PS after block relative to the pre-block condition.

The PS/DS-ratio was used as a measure of any change in nerve conduction that persisted after block. In the study done by Ackermann et al. [10] the PS/DS ratio, in 3/5 animals, had reduced by 50% after 30 seconds and the nerve was completely damaged in all 5 animals after 60 seconds of cumulative DC delivery. In that study, the nerve conduction did not recover even after 30 minutes after DC block application and was presumed to indicate permanent nerve damage [10]. In the present study, the PS/DS ratio remained consistent and no trends were observed in the PS/DS ratios over the duration of the experiment.

One of the concerns of using the anodic phase to balance the cathodic charge in the electrode-electrolyte interface was that crosstalk between the KHFAC and CBDC electrodes could cause the block to fail during the recharge phase. We did observe this effect during the preliminary phase of the experiment when we used two current-controlled waveform generators, one for the CBDC and the other for the KHFAC block. This effect was eliminated by using voltage-controlled KHFAC waveforms. Additionally we used the DC filter circuit to minimize unintended DC contamination of the KHFAC electrode [28]. An added benefit of using the DC filter circuit was that the high frequency contamination of the CBDC electrode was minimized.

It was important to keep the CBDC anodic current below 0.2 mA. While higher currents allowed shorter anodic recharge phases, the limit of 0.2 mA was determined in preliminary experiments as the value that limited unwanted activation of the nerve during this phase. Activation could either be caused by virtual cathodes distally to the CBDC electrode, anodic break for off-ramps with short durations, or crosstalk from the KHFAC waveform. The crosstalk was minimized by ensuring that each generator was electrically floating, resulting electrically in a star connection at the acute nerve preparation, the only point where all four electrodes came together. Although the DC filter circuit helped to minimize HF crosstalk, there was still the potential for capacitive and inductive coupling between cables connecting the electrodes to the waveform generators. Keeping the anodic recharge current at the said levels allowed a reasonably short recharge phase without nerve activation during the application of both block waveforms.

There was no need to change the DC block amplitude once the optimal current for blocking the onset response had been identified. Once set, optimal block parameters were generally kept unaltered for the remainder of the experiment. We investigated shortening the CBDC ramps in animal 4 but this produced neural activity and we did not pursue this alternative further.

We do not know what caused the loss in charge injection capacity for the Pt-black CBDC block electrodes and assume that the loss was a cumulative effect due to bending of the electrode during implantation and explantation, deposition of proteins on the electrode surface, and the rinsing of the electrodes under water. It does not appear that Pt-B is mechanically stable enough for chronic use. A future chronic study would require the use of a more durable material.

The 8.2H inductors were achieved by connecting only to the primary coil of signal transformers whose secondary side was intentionally left open and the secondary coil's ends insulated from each other. For waveforms in the kilohertz range, these transformers of about 1 cubic inch in volume resulted in a direct current impedance between 600 and 800 Ω caused by the winding of primary side, while providing an impedance of more than 200 k Ω for HF signals at 20 kHz, again measured only through the primary side. We understand that inductors of 1 cubic inch in volume are still too large for implantation and thus only see them as a first step towards an implantable solution that would allow the filtering of unintended DC contamination, while at the same time providing large enough impedances to KHFAC waveforms in order to prevent an attenuation there. Using the same approach, we

tested signal transformers of about 1 cm³ in volume in preliminary experiments and saw that their HF impedance at 20 kHz was only 1.2H, or about 21kΩ for HF signals, causing about 5% of the HF waveform to short through the inductor in addition to the DC. In order to have the maximal KHFAC amplitude available, we used the significantly larger 8.2H inductors in the DC-filter circuit that connected the HF waveform generator to the electrodes. Further studies will investigate the use of such secondary-side-open-transformer inductances for the reduction of unintended waveform components in neural applications in research and translation.

An important next step would be testing of this technique in a chronic animal study with implanted electrodes for KHFAC and CBDC block. Our goal in this study was to provide evidence that a subsequent chronic study using a similar approach would have a high probability for success with regard to efficacy (electric nerve block without an onset response) and safety (no change in nerve conduction in an acute setting).

Conclusions

This study demonstrated that an electric nerve block can be initiated without an onset response and maintained for tens of minutes without a decrease in nerve response following termination of block. We were able to achieve a reduction of the KHFAC onset response using a distally placed charge balanced DC (motor) block in eight out of eight animals. A randomized study of four animals showed statistically significant differences for both onset force height and area, for each animal, as well as across the four animals as a group. The success of this proof-of-concept study suggests that it may be possible to achieve electrical nerve conduction block without an onset response by using a combined KHFAC and CBDC approach, and that this approach may be useful for repeated applications of this method for at least tens of seconds.

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Figure 1. Comparison between nerve conduction block achieved with KHFAC (A) and charge balanced DC (B) waveforms. While an intense neural firing causing a strong muscle contraction (onset response) is characteristic for nerve block achieved with KHFAC waveforms, ramped DC waveforms allow for a nerve conduction block without producing any additional activity when appropriately ramped. Note that the recharge phase (seconds 20 to 70 in B) does not block nerve conduction but dominates the overall duration of the CBDC block trial. PS and DS indicate force comparison from proximal and distal stimulation to assess nerve conductivity after block. Both block waveforms do *not* change the nerve conductivity after block.

Figure 2.

Electronic setup and animal preparation. Four electrodes were acutely implanted on the rat sciatic nerve. These electrodes were, from proximal to distal, proximal stimulation (PS), KHFAC block, CBDC block, and distal stimulation (DS). The forces evoked by the gastrocnemius muscle were measured to determine nerve activation and block. The waveform supplied to each of the electrodes was provided by a stimulator with its own dedicated power supply, providing a completely floating setup. The DC-filter circuit (two capacitors with optimized DC-shunting inductors; US-Pat 14/275,446) between the KHFAC generator and HF electrode ensured that only KHFAC waveforms reached the HF electrode without unintended DC contamination.

Figure 3.

Stimulation sequence and expected force measurement over time. The 2Hz PS (grey) and 1Hz DS (black) stimulation signals were easily differentiated from each other and provide information on the nerve conductivity before, during and after the combined KHFAC+DC block. The DC block amplitude was increased linearly for two seconds (cathodic polarity), followed by a plateau of variable duration (2–10s), followed by a linearly decreasing amplitude to zero. This cathodic DC block phase was followed by an anodic recharge phase, providing zero net charge over the entire waveform. Note that the ramped cathodic DC is expected to initially cause partial block (as indicated here by partially reduced PS twitch forces).

Figure 4.

Forces caused by the onset response at the initiation of KHFAC-only nerve block (A) can be significantly reduced with an additional, distally placed, CBDC block (B). Twitch forces evoked by proximal stimulation (PS) was completely blocked by both forms of nerve block. The arrow indicates where the on-ramp rate is increased to reach the plateau current faster.

Figure 5.

Example of three side effects observed with sub-optimal waveform parameters. Black arrow indicates KHFAC onset peak force being just above the force for a PS twitch because the DC plateau was not high enough. Grey arrow indicates part of the onset response not blocked because the DC block was not long enough and the overall KHFAC onset was longer than five seconds. Dashed black arrow indicates small onset firing caused by the first part of the CBDC on-ramp being too steep.

Figure 6.

Reduction of the onset **force** across animals and comparison to a PS twitch force height (far right). A statistically significant reduction was achieved in each one of the animals as well as across all animals combined (* $p < 0.001$). In this notched box and whisker plot, the median forms the midline of the notch which indicates the 95% confidence interval around the median. The box itself covers the interquartile range (IQR) from the 25 to the 75 percentile of the data. The whiskers extend from the edges of the box to 1.5 times the IQR to cover 99.3% of the data. Points outside the whiskers are likely statistical outliers, indicated by a small asterisk.

Figure 7. Reduction of the **area** under the onset-force-over-time graph. Comparison across animals and to PS twitch (far right). A statistically significant reduction was achieved in each animal as well as across all animals combined (* $p < 0.01$, ** $p < 0.05$). In this notched box and whisker plot, the median forms the midline of the notch which indicates the 95% confidence interval around the median. The box itself covers the interquartile range (IQR) from the 25 to the 75 percentile of the data. The whiskers extend from the edges of the box to 1.5 times the IQR to cover 99.3% of the data. Points outside the whiskers are likely statistical outliers, indicated by a small asterisk.

Figure 8.

Nerve conductivity for all animals shown vs. cumulative time spent in the cathodic portion of the CBDC waveform (A) and shown vs. cumulatively injected cathodic DC charge during combined KHfAC+CBDC block (B). The PS/DS-ratio, describing the nerve conductivity after block between proximal and distal stimulation electrode, did not significantly change from 1, indicating no undesirable effects for nerve viability (avg. PS/DS). Underlying PS/DS-data is the same in A and B, difference is depiction vs. DC block time (A) and depiction vs. injected DC charge (B; avg. Q). The 60s of cumulative DC delivery in (A) indicate the point in time at which Ackermann et al. [10] reported complete loss of nerve conduction (PS/DS=0) showing a major problem with conventional DC block to mitigate the KHfAC onset response. The average values for PS/DS, cathodic DC time (avg. t_{DC}), injected charge Q and cathodic DC current (avg. I_{DC}) varied from animal to animal and are indicated for each case in (A) and (B).

Table 1

Average parameters across all successful combined CBDC+KHFAC block trials and cumulative over time.

animal	CBDC block parameters (per trial)				Values for the duration of the experiment			
	Amplitude of cathodic plateau (mA)	Duration of entire cath. phase (s)	Cath. charge injected to block(mC)	cumulative injected cath. charge (mC)	cumulative cathodic DC block time (s)	PS/DS ratio throughout experiment	initial PS/DS-ratio at the beginning	final PS/DS-ratio at the end
1	1.7±0.3	10.9±1.0	11.8±1.8	342.6	318.8	1.02±0.02	1.01	1.01
2	2.5±0.1	6.7±0.9	12.1±2.0	715.3	377.0	0.98±0.03	1.02	0.99
3	1.8±0.3	24.3±0.3	15.7±0.9	267.6	440.0	0.97±0.02	0.97	0.95
4	2.4±0.1	22.2±4.3	9.2±1.0	555.9	1563.4	1.00±0.02	0.99	1.00

Table 2

Optimal parameters defining the KHfAC and CBDC waveform for each animal.

CBDC								
	KHFAC (f=20kHz)							
animal	Amplitude (V)	Plateau amplitude (mA)	Duration cathodic on-ramp (s)	Duration cathodic plateau (s)	Duration cathodic off-ramp (s)	Duration Recharge on-ramp (s)	Duration Recharge anodic plateau (s)	Duration Recharge off-ramp (s)
1	5.0	- 1.8	6.0	2.6	2.0	1.0	47.5	1.0
2	8.0	- 2.5	2.0	3.0	1.0	1.0	44.3	1.0
3	5.0	- 1.5	20.0s: -0.8 mA, 2.0s: -1.5 mA *	2.0	2.0	4.0	85.2	1.0
4	8.0	- 2.4	16.0s: -0.4 mA, 2.0s: -2.4 mA *	1.0	3.0s: -0.6 mA, 11.3s: 0 mA *	4.0	63.5	10.0

* Notation for 2-step ramps: *NN* s: -*OO* mA, *PP* s: *QQ* mA; *NN* seconds to reach *PP* mA, then *PP* seconds to reach *QQ* mA plateau.