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Frequency and amplitude transitioned waveforms mitigate the onset response in high frequency nerve block

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Abstract

High frequency alternating currents (HFAC) have proven to be a reversible and rapid method of blocking peripheral nerve conduction, holding promise for treatment of disorders associated with undesirable neuronal activity. The delivery of HFAC is characterized by a transient period of neural firing at its inception, termed the “onset response”. The onset response is minimized for higher frequencies and higher amplitudes, but requires larger currents. However, complete block can be maintained at lower frequencies and amplitudes, using lower currents. In this in-vivo study on whole mammalian peripheral nerves, we demonstrate a method to minimize the onset response by initiating the block using a stimulation paradigm with a high frequency and large amplitude, and then transitioning to a low frequency and low amplitude waveform, reducing the currents required to maintain the conduction block. In five of six animals it was possible to transition from a 30 kHz to a 10 kHz waveform without inducing any transient neural firing. The minimum transition time was 0.03 sec. Transition activity was minimized or eliminated with longer transition times. The results of this study show that this method is feasible for achieving a nerve block with minimal onset responses and current amplitude requirements.

Keywords

High frequency nerve block; functional electrical stimulation; onset response; in-vivo model

INTRODUCTION

The delivery of high frequency alternating currents (HFAC) has proven to be a reversible and rapid method of blocking peripheral nerve conduction [1–8]. HFAC in the frequency range of 1 – 40 kHz [9–10], delivered through a cuff electrode in direct contact with a peripheral nerve, has been shown to reversibly block the propagation of action potentials [7,11]. The typical HFAC amplitude ranges between 1 – 10 V (peak to peak) in order to achieve complete block and is dependent on the frequency used and the electrode to nerve interface [8–9]. Block is established in less than 100 ms [11] and is completely reversible when the HFAC is turned off, as the nerve returns to full conductivity within approximately one second [5,7–8]. The fast onset of the conduction block and the quick reversibility makes HFAC block appealing for potential clinical uses. Recent studies in rats [8,12–14], frogs [7],

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and cats [6,9,15] have shown that HFAC is an effective method of blocking peripheral nerve conduction.

One undesirable aspect of HFAC nerve block is the initial volley of action potentials when the HFAC is first turned on, termed the “onset response”. The onset response has been demonstrated in animal studies using single fiber recordings [4–5], urethral sphincter pressure [6,9,15], muscle force [7–8,12–14], and in computer simulations [7,10,12,16–17]. The onset response can be separated into two phases [14]. Phase I is an initial burst of action potentials when the HFAC is initiated. Phase I is always present whenever HFAC is delivered, and typically consists of a few action potentials (~1 to 6) generated as rapidly as physiologically feasible [10,11]. Phase II, if present, follows immediately after Phase I and generally consists of a prolonged but lower intensity nerve activity [8,14]. However, Phase II activity can be minimized or eliminated by proper selection of electrode design and HFAC waveform parameters [8,14]. It has been established that higher frequencies and higher amplitudes result in minimization of the onset response [8,14].

HFAC block requires amplitudes above a minimum “block threshold” in order to completely block a peripheral nerve [7,8]. The motor “block threshold” is defined as the lowest amplitude at which all motor axons in the nerve are blocked. For a given mammalian electrode- to-nerve interface, the block threshold increases monotonically for increasing frequencies [8–10,12,18]. Nerve conduction remains blocked as long as the HFAC amplitude is maintained at or above the block threshold. It is desirable to minimize the HFAC amplitude used in order to minimize the amount of charge injected into the nerve [19] and to minimize the power requirements of a possible clinical system. This can be achieved at the lower frequencies with lower block thresholds. However, initiating the block at these lower frequencies leads to the largest onset responses with the most Phase II activity.

There is a tradeoff between minimizing the onset response and minimizing the voltage/current required to block. Specifically, the onset response is minimized with high amplitude and high frequency, whereas the voltage/current is minimized at the lower frequencies where block thresholds are lower. As a result, it is desirable to consider utilizing a waveform that minimizes the onset response by initiating the block with a high frequency and large amplitude and then transitions to a low frequency, low amplitude waveform in order to reduce the voltage/current required to maintain block. Minimizing the onset response in such a way would increase the number of relevant human applications for which HFAC could be utilized. Transitioning to a lower frequency and amplitude after achieving minimal onset would be important for minimizing power consumption, and possibly for ensuring safe waveform delivery since lower currents are generally associated with a safer stimulation protocol [19].

The goal of this study was to evaluate whether the transition in frequency and amplitude during HFAC block could be accomplished without inducing any additional nerve activity beyond the onset response. Previous studies have indicated that rapid changes in either amplitude or frequency often produced bursts of activity in the nerve [8]. We hypothesized that a smooth simultaneous transition of both frequency and amplitude could be accomplished without activating the nerve if the transition period was sufficiently long. Furthermore, we hypothesized that less activity would be induced by a transition from a high amplitude to a low amplitude than vice versa. This type of amplitude transition would be naturally coupled with the frequency transition from high to low, since block thresholds also decrease as the HFAC frequency is lowered [8].

METHODS

Animal and Surgical Procedure

Frequency and amplitude transitions were evaluated in ten adult Sprague-Dawley rats under institutional approval. The animals were anesthetized with intraperitoneal Nembutal (pentobarbital sodium). The surgical procedure has been described previously [8]. The sciatic nerve was carefully exposed through a postero-lateral incision and the sural and common peroneal nerves were cut. The gastrocnemius-soleus muscle complex was exposed and its insertion into the calcaneus was severed. The calcaneal tendon was attached to a force transducer that was pre-tensioned with approximately 1–2 Newtons. The opposite hind leg was clamped down.

Electrical Stimulation and HFAC Block

Two bipolar platinum cuff electrodes were positioned along the sciatic nerve as illustrated in Figure 1. Each electrode had two 1 mm wide contacts with 1 mm separation between contacts [14,18]. The proximal electrode was used to deliver suprathreshold monophasic square pulses from an isolated current source (Grass S88 Stimulator, Grass Technologies, West Warwick, RI, USA) at a rate of 1 Hz. The distal electrode was used to deliver the HFAC waveform, which was generated by an arbitrary waveform generator (Wavetek 395, now Willtek Communications GmbH, Ismaning, Germany). Labview software (National Instruments, Austin, Texas, USA) was used to control the Wavetek output to simultaneously sweep the frequency and ramp the amplitude as illustrated in Figure 1.

The HFAC waveform used in each trial consisted of three phases (Figure 1). First, the HFAC waveform was turned on at 30 kHz at either a high amplitude of 10 Vpp or a low amplitude of 3 Vpp (the 30 kHz block threshold was in the range of 5 – 7 Vpp). The frequency and amplitude were held constant during this first phase. The second phase consisted of the frequency and amplitude transition with the frequency sweeping from 30 kHz to 10 kHz at a constant linear rate and the amplitude ramping linearly to its final value (described below). The duration of the second phase was termed the *transition time*. The third phase began at the end of the transition time, once the frequency and amplitude reached their final values. During this third phase, the frequency was maintained at 10 kHz and the amplitude was held at either 10 Vpp or an amplitude just above the 10 kHz block threshold (measured experimentally in each animal). Three different *amplitude transitions* and four different *transition times* were tested during each experiment. The frequency of the waveform was always swept from 30 kHz to 10 kHz. The three *amplitude transitions* tested were; A. “High to low”, from a high amplitude (10 Vpp) to a low amplitude (just above 10 kHz block threshold). B. “Low to high”, from a low amplitude (3 Vpp) to a high amplitude (10 Vpp). C. “High to high”, from a high amplitude (10 Vpp) to a high amplitude (10 Vpp). The transition times are described below.

Prior to evaluating the waveform transition response, block thresholds were determined for both 10 kHz and 30 kHz HFAC [8]. During a block threshold trial, suprathreshold stimulation pulses were delivered through the proximal electrode generating maximal force twitches in the muscle. The proximal stimulation was delivered throughout the trial to monitor the degree of conduction block. For each frequency, the HFAC was turned on at 10 Vpp. Once the muscle force returned to baseline and no muscle twitches were observed, indicating complete block, the amplitude was then gradually decreased in 1 V decrements (at 1 s intervals per step) until muscle twitches were first observed. The lowest amplitude at which complete conduction block was still maintained was defined as the block threshold. The low amplitude used in the third phase of the transition waveform at 10 kHz was chosen to be 1 Vpp above the 10 kHz block threshold.

Preliminary experiments were performed in two animals to map the range of *transition times*, as a guide to the randomized experiments. Randomized and repeated trials (three repeats) were performed in seven animals. A follow up experiment of transition times longer than the longest times used in the randomized experiments were performed in one animal. The sweep times used during the randomized experiments ranged between 0.03 seconds to 60 seconds. The sweep times were determined during preliminary trials in each animal. Transition waveforms were tested that swept the frequency from 30 kHz to 10 kHz and ramped the amplitude from a high amplitude of 10 Vpp to a low amplitude just above the 10 kHz block threshold. Transition times, starting with 10 seconds and increasing to 60 seconds in 10 second increments, were tested in individual trials to determine if a successful transition could be achieved without generating nerve activity during the transition. If a successful transition was achieved, the transition time used became the maximum of the 4 transition times used in the series. Of the seven animals in the randomized series, transition times of 0.03, 0.1, 1, and 10 seconds were tested in four animals; 0.1, 1, 10, and 20 seconds were tested in two animals; and 1, 10, 30, and 60 seconds were tested in one animal. Sweep times up to 180 s were evaluated in the one follow up experiment.

Repeated and randomized trials were conducted in seven animals, to determine the influence of the amplitude transition and the transition time on the magnitude of the onset response generated during the transition phase of the HFAC waveform, called the "*transition activity*". A total of twelve trials were included in each randomized section to test all combinations of the three amplitude transitions and four transition times. The sections were repeated three times for a total of 36 trials per animal. At the end of every sixth trial in the series of randomized trials, a control trial was performed where two bursts of 10 kHz HFAC were delivered to the nerve for approximately 3 seconds each with a 10 s gap between the two bursts. The first burst of HFAC was delivered at the high amplitude, 10 Vpp, while the second burst was delivered at the low amplitude, just above the 10 kHz block threshold. The control trials provided a measure of the 10 kHz onset response at two amplitudes, without the frequency and amplitude transition, for comparison to the nerve activity generated during the transition. There was a one minute rest between all trials.

Data Analysis

To compare the transition activity over all transition times and amplitude transitions, the maximum, or peak, muscle force (N) and the force-time integral, or area (N.s), of the transition activity were determined for each trial [8,14]. The force-time integral was calculated from the beginning of the transition (start of the second phase of the waveform) to when the HFAC waveform was turned off (end of the third phase).

Statistical analysis was carried out with a commercial software package (JMP, SAS Institute Inc.) A one-way fixed effects analysis of variance (ANOVA) model was applied to the data sets to test the null hypothesis of equality of means. The control variables were animal number (n=6), transition sweep times (n=4) and amplitude transitions (n=3). The tested response variables were the peak force and the force-time integral. To analyze across all animals, transition times were ordered from low to high. The Tukey Kramer HSD (Honestly Significant Difference) test was carried out between groups.

RESULTS

Complete HFAC conduction block was achieved in the sciatic nerve of all ten animals at both 10 and 30 kHz. Block thresholds were in the range of 2 to 5 Vpp for 10 kHz (mean 3.2, SD 1.1) and 5 to 8 Vpp for 30 kHz (mean 6.5, SD 1.1). The onsets for 30 kHz were smaller than those for 10 kHz (Figure 2). Non-optimal frequency transitions resulted in significant transition activity (bottom trace Figure 2). The two preliminary animals demonstrated that

frequency amplitude sweeps could be accomplished without any transition activity over a range of transition times (0.03 s to 60 s) for amplitude sweeps from “high to low”. The randomized set of 36 trials per animal was completed in six animals. Only two repeats (24 trials) could be completed in one animal. Therefore, this animal was excluded from the results, though there were successful transitions in some of the 24 trials. The results show that combined frequency and amplitude ramps are successful in initiating HFAC block at a high frequency and amplitude and then transitioning to a lower frequency and amplitude. The success is dependant on both the type of amplitude ramp and the transition time as discussed below.

Amplitude ramps

The “high to low” amplitude transitions resulted in the lowest level of transition nerve activity compared to the two other amplitude transitions. Figure 3 shows the effect of the transition waveform for three different amplitude ramps. For the “low to high” and “high to high” amplitude transitions, nerve activity was observed during the transition phase as the frequency approached 10 kHz. Transition activity was not observed during the “high to low” amplitude transition. Figure 4 presents the data for all animals as a function of the three amplitude ramp groups and includes all trials. The ANOVA results show that the differences between means are significant at $p<0.001$. The Tukey Kramer HSD tests on the transition peak force and onset area show that amplitude ramp “low to high” is significantly different from amplitude ramp “high to low” for onset area ($p<0.01$) as well as for peak force ($p<0.05$). It is not significantly different when compared to the amplitude ramp “high to high”.

Transition times

Longer transition times typically resulted in a smaller transition onset response. Figure 5 illustrates the transition activity response to four different transitions times tested in a single animal transitioning from a high (10 Vpp) to low (4 Vpp) amplitude. There is transition activity for the shorter transition times of .03 s and 0.1 s but none for both 1 s and 10 s. Activity at 0.1 s is less than for 0.03 s. Figure 6 presents box plots of peak force and onset area for all the data versus the four transition times ordered from low to high. Both output measures decrease with longer transition times and are smallest for the longest transition times. The Tukey Kramer HSD test shows that the two longer transition times have significantly lower peak forces and onset areas compared to the two shorter transition times ($p<0.05$)

Frequency and amplitude transitions

Successful transitions were obtained in five of six animals. The transition waveform successfully swept the HFAC frequency from 30 kHz to 10 kHz with no recordable muscle activity during the transition. This success was dependent on both the type of amplitude transition and the transition times.

Figure 7 A shows all 216 data points for all six animals plotted as successes or failures of the transition waveform. Filled markers indicate successful transitions without any transition activity. Successful transitions were obtained in animals 1 to 5. Two trends were observed for the two main input variables of amplitude ramp and transition time. Most of the successful trials were in the “high to low” group (36 of 72 trials in 5 animals). Only a few trials were successful in the “high to high” (11 of 72 trials in 3 animals) and “low to high” (3 of 72 trials in 2 animals).

The shortest transition time in one animal (#3) was 0.03 s. Once a specific transition time showed success, most transitions times longer than that were also successful. In the sixth

animal, 60 seconds (the longest transition time tried) still resulted in some onset activity. A follow up experiment in a different animal (not part of the randomized group) had a similar result for a 60 s transition time. However, a transition time of 180 s showed successful transitions without any muscle activity.

Even in the trials classified as a failure, the peak force and area both showed the trend of being less in the “high to low” amplitude group as well as trending lower for longer transition times. The latter is illustrated in Figure 7 B which plots the peak force values (averaged for the 3 repeats) versus ordered transition times for all six animals for the *“high to low” amplitude ramp group*. In three animals (# 1,3, and 5) the transition peak force is essentially zero. There is extremely low activity for the shortest transition times and then no activity for the successful transition times (#1 has 7 of 12 successes, # 3 has 9 of 12 and #5 has 12 of 12). The other animals (#2, 4, and 6) show large decreases in peak force for longer transition times and there is no transition activity for the successful trials in 2 animals (#2 and 4). The one animal classified as a failure (# 6) also shows a large decrease in transition peak force at the longest transition time of 60 s compared to shorter times.

DISCUSSION

In this study we have successfully demonstrated the use of an experimental technique which delivers HFAC with a minimal onset response and maintains it efficiently. High-amplitude, high-frequency HFAC waveforms produce smaller magnitude and shorter duration onset responses when compared to low-amplitude, low-frequency HFAC waveforms [8]. However, higher-frequency waveforms require greater HFAC amplitudes to achieve conduction block since the block thresholds are higher with increased frequency [8]. In order to take advantage of the smaller onset response characteristics of a high-frequency, high-amplitude HFAC waveform and the low power characteristics of the low-frequency, low-amplitude HFAC waveform, we created a waveform that began at 30 kHz, 10 Vpp then linearly swept the frequency to 10 kHz and ramped the amplitude down to a voltage just above the block threshold at 10 kHz. Given the right amplitude parameters and transition durations, the waveform was successful in transitioning to 10 kHz without initiating any additional nerve activity after the initial brief onset response at 30 kHz. While transitioning the HFAC amplitude from high amplitude at 30 kHz to low amplitude at 10 kHz, the transition could be performed with a minimal transition time of 0.03 seconds without initiating additional nerve activity. Successful transitions were obtained in five out of six animals. The experiments were performed with bipolar electrodes, which we have recently demonstrated produce excellent HFAC nerve block [18]. Tripolar electrodes may potentially produce lesser onset activity which would make the waveform transition easier. The waveform transition technique shows promise as a possible method to minimize the onset response for clinical applications.

The results presented in Figures 3 through 7 show that the magnitude and duration of nerve activity measured during the transition depended on the transition time and the amplitude transition conditions of the waveform. The variability in the transition times used and the waveform conditions required to eliminate activity generated during the transition could be due to variability between animals, the surgical preparation, or the position of the blocking electrode [8, 22]. The results indicated that ramping the HFAC amplitude from a high amplitude to a low amplitude was more likely to occur without generating nerve activity was generated during the transition. This is clinically applicable since the block threshold at lower frequencies is lower than at higher frequencies. In addition to the six animals presented in the results, the transition waveform was tested on a subsequent animal exhibiting a similar nerve response to that of the one animal where a 60 second transition time was insufficient to eliminate the transition onset. In this animal, a transition time of 180

seconds was long enough to eliminate the activity observed during the transition, suggesting that it is possible to successfully transition the frequency and amplitude without initiating any activity in the nerve during the transition using sufficiently long transition times. Although a longer transition time means the waveform is slower to reach the final low-frequency and low-amplitude parameters, this is expected to be a small percentage of the total duration of block, which could be tens of minutes to many hours when this type of block is used for pain relief.

We postulate that the success of the waveform to transition from a high-frequency to a low-frequency without initiating activity in the nerve and muscle is predominantly due to the rate of change of the charge (ΔC) being delivered to the nerve during each succeeding half-cycle of the sweep. As the frequency is lowered, each half-cycle increases in width and area (charge). We hypothesize that there is a threshold for ΔC above which the nerve starts firing. The threshold is different for different axonal sizes. However, our successful experimental outcome is based on the absence of activity in *all motor fibers*. When the waveform transition occurs over a long transition time, ΔC is low and the nerve is non-responsive to these smaller changes. Similarly, when the amplitude transitions from a high-amplitude to a low-amplitude, Δ C is less than when the amplitude is transitioned from a low-amplitude to a high-amplitude or if the amplitude remains high. Therefore, a more gradual increase in charge is more likely to accomplish the frequency and amplitude transition without initiating nerve activity. The amplitude ramps and the transition times result in specific ΔCs for each trial. Figure 8 demonstrates that for a transition time of 10 s, the ΔC effect is shown by the nerve firing first in the “low to high” amplitude group at ~26 kHz (where the increasing amplitude ramp adds to an increasing ΔC), the “high to high” at ~16 kHz and the ”low to high” at ~15 kHz (where the decreasing amplitude ramp counteracts an increasing ΔC).

It is also interesting to note that transitioning the HFAC waveform from a high amplitude, approximately 1.5 times the block threshold at 30 kHz, to an equally high amplitude, approximately 3 times the block threshold at 10 kHz, results in more activity during the transition than transitioning between amplitudes that are both approximately 1.5 times the block threshold of their respective frequency. This implies that it is not the blocked region of the nerve that is initiating this transition activity. It is likely that this activity is generated at sites on the nerve flanking the blocked region (the blocked region is directly under the electrode). The large field intensity produced by the high-amplitude at the site of the electrode also produces a lesser, but significant, “virtual electrode” field intensity at the edges of the insulating nerve cuff which do not exist at lower field intensities associated with the lower stimulation amplitudes [14,23]. This “virtual electrode” field intensity is likely to be below block threshold, and may induce nerve firing [14,23]. Computer simulations and single fiber recordings have demonstrated that neurons subjected to HFAC amplitude below block threshold undergo rapid firing [5,10,14]. Therefore, the intensity of these subthreshold fields would increase with an increase in HFAC amplitude and more activity would be observed in the nerve and muscle during an amplitude transition.

HFAC block offers potential clinical value in the treatment of diseases and disorders marked by unwanted motor and sensory nerve conduction. However, the clinical effectiveness of such a treatment depends on the ability to mitigate the undesirable neural activity initiated at the onset of the HFAC. Because the onset response is likely to cause strong muscle contractions and pain, the possible clinical applications for which HFAC could be used would be limited. A short duration onset response would likely be acceptable for treating conditions that do not involve intact sensory pathways, such as chronic spasticity control or bladder voiding [15,20] for spinal cord injury [14]. Additionally, a brief onset response might be permissible for conditions where the onset response was an acceptable compromise in order to achieve significant clinical gain, such as in the treatment of chronic pain

applications or in treating conditions where the HFAC block is infrequently turned on and the onset rarely experienced. The lesser charge injection required for the low frequencies may help to promote safer stimulation [19]. For clinical applications, it is desirable to minimize the charge delivered to the nerve to minimize the power requirements of a stimulation system, and possibly to promote both nerve health and electrode longevity [19].

Other approaches for eliminating the onset have been presented in the literature. Based on their computer simulations of a Hodgkin-Huxley (Hodgkin and Huxley 1952) unmyelinated giant squid axon, Tai et al. predicted that an amplitude ramp, starting from zero amplitude and increasing to an amplitude sufficient to induce block, could be used to eliminate the onset response [21]. However, Miles et al. showed experimentally that an amplitude ramp was unsuccessful and the degree of nerve onset activation was in fact increased during the amplitude ramp [22]. Computer simulations of a mammalian myelinated nerve model suggests that there is an amplitude region below block threshold, where the HFAC produces significant and prolonged nerve activity [10]. This activity occurs when the amplitude of the HFAC is approximately 50 – 70% of the block threshold [10]. Ackermann et al. have demonstrated ways to minimize the onset activity by manipulating the nerve cuff electrode geometry of the HFAC blocking electrode as well as the HFAC waveform amplitude [14]. They found that for the range of bipolar separation distances and monopolar contact lengths tested, a bipolar electrode with 0.5 mm spacing or a monopolar electrode with 0.25 mm or 4 mm contact length produced the smallest onset. Additionally, they presented data that confirmed the work of others which indicated that higher HFAC waveform amplitudes resulted in decreased magnitude and duration of the onset response. However, these electrode and waveform amplitude manipulations did not completely eliminate the onset response.

This study presents a method to minimize the onset response of the nerve to the HFAC waveform while delivering a low-amplitude, low-frequency conduction block for long term safety in clinical applications. Initiating the waveform at a high frequency produces an onset with smaller magnitude and shorter duration than low frequency waveforms of similar amplitude. Maintaining the HFAC block after the sweep at the lower frequency, which requires a lower amplitude to block, reduces the amount of power required to block the nerve and may promote preservation of the nerve tissue health and electrode viability.

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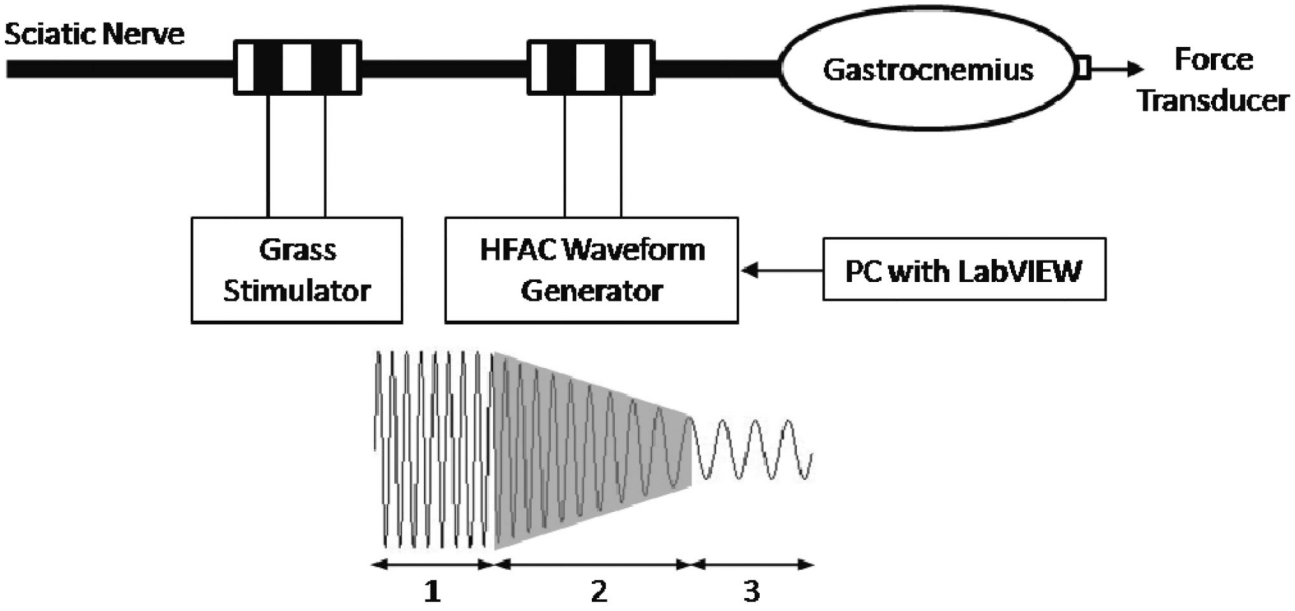

Figure 1.

Top: Experimental setup showing the proximal stimulating and blocking cuff electrodes on the sciatic nerve. Bottom: An example test waveform showing the three phases, demonstrating a transition from 30 kHz to 10 kHz and from a high to a low amplitude (one of the three amplitude transitions that were tested). (1) Phase 1: the frequency was held constant at 30 kHz while the amplitude was high. (2) Phase 2: the frequency and amplitude transition with the frequency sweeping from 30 kHz to 10 kHz at a constant rate and the amplitude ramping linearly to its final value. The duration of the second phase was termed the *transition time* (grayed region). (3) Phase 3: the frequency was maintained at 10 kHz and the amplitude was held at a low value.

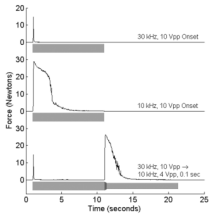

Figure 2.

Example of a Phase I only onset in response to a 30 kHz, 10 Vpp sinusoid (*top*) compared to a prolonged Phase I + II onset response at 10 kHz, 10 Vpp (*middle*). An unsuccessful frequency and amplitude transition (0.1 s) resulted in significant transition activity (*bottom*). The light gray bars below the traces indicate the delivery of the HFAC waveform. In the bottom figure, the transition is indicated by the dark gray region.

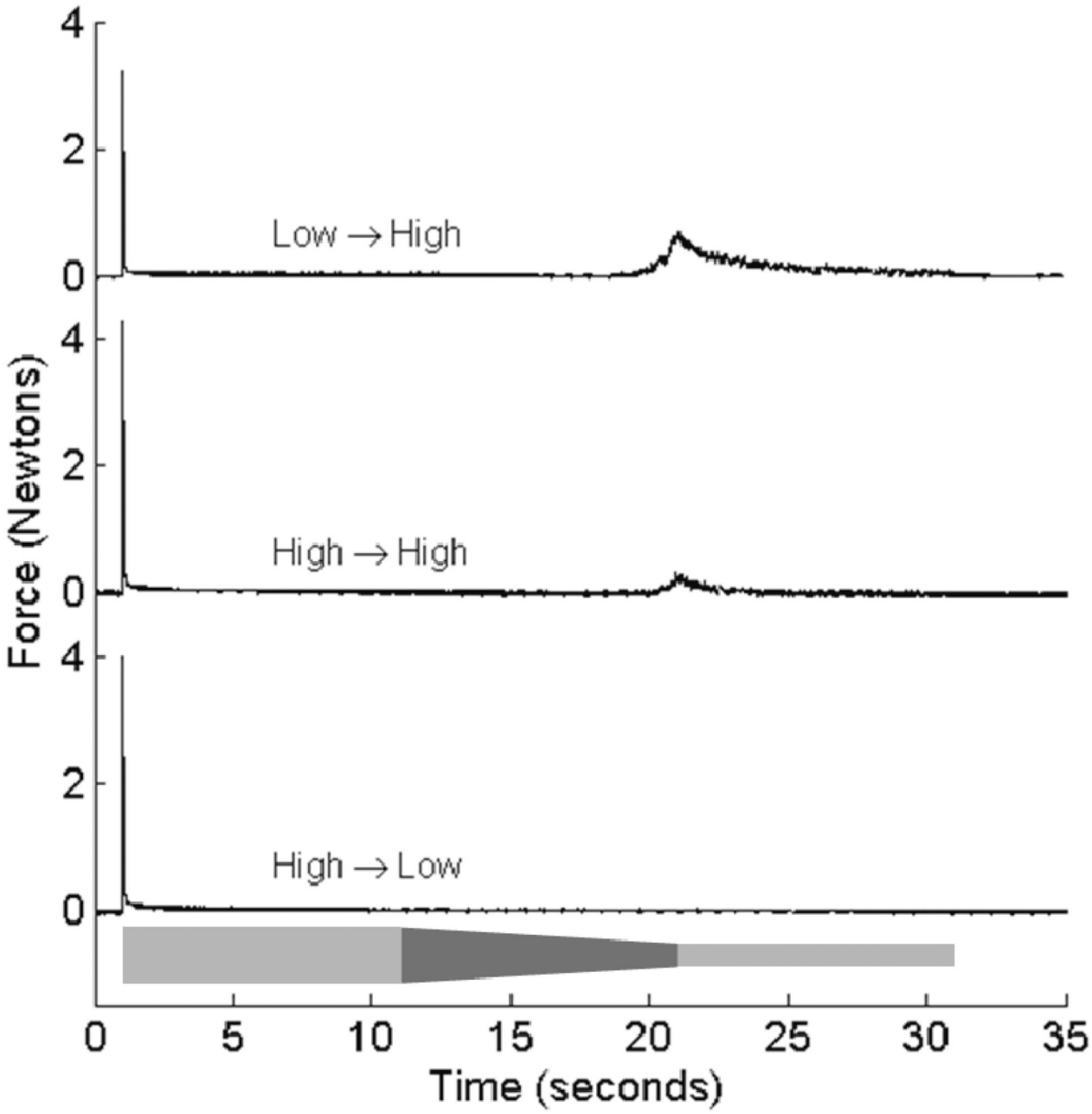

Figure 3.

Examples of the transition activity response to three different amplitude transitions tested in a single animal with a transition time of 10 seconds. For the low (3 Vpp) to high (10 Vpp) (*top*) and high (10 Vpp) to high (10 Vpp) (*middle*) amplitude ramps, transition activity occurred. This transition activity was not observed during the high (10 Vpp) to low (4 Vpp) (*bottom*) amplitude transition. The light gray bar below the bottom trace indicates the HFAC waveform with the transition in the dark gray region.

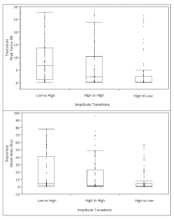

Figure 4.
The combined data from all animals and all transition times presented as box plots (median, lower and upper quartile and minimum and maximum), comparing the transition onset peak force (*top*) and area (*bottom*) across all three amplitude transitions. The transition onset peak force and area are smallest for the high to low amplitude transition.

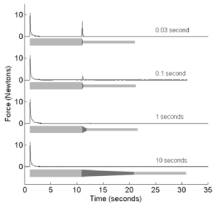

Figure 5.

Comparison of the transition onset response to four different transitions times tested in a single animal with an amplitude transition from high (10 Vpp) to low (4 Vpp). Transition activity was observed at the end of a 0.03 second transition time (*top*). Longer transition times result in less activity during the transition until no activity was observed with transition times of 1 s and 10 s (*bottom*). The gray bars below each trace indicate the waveform timing.

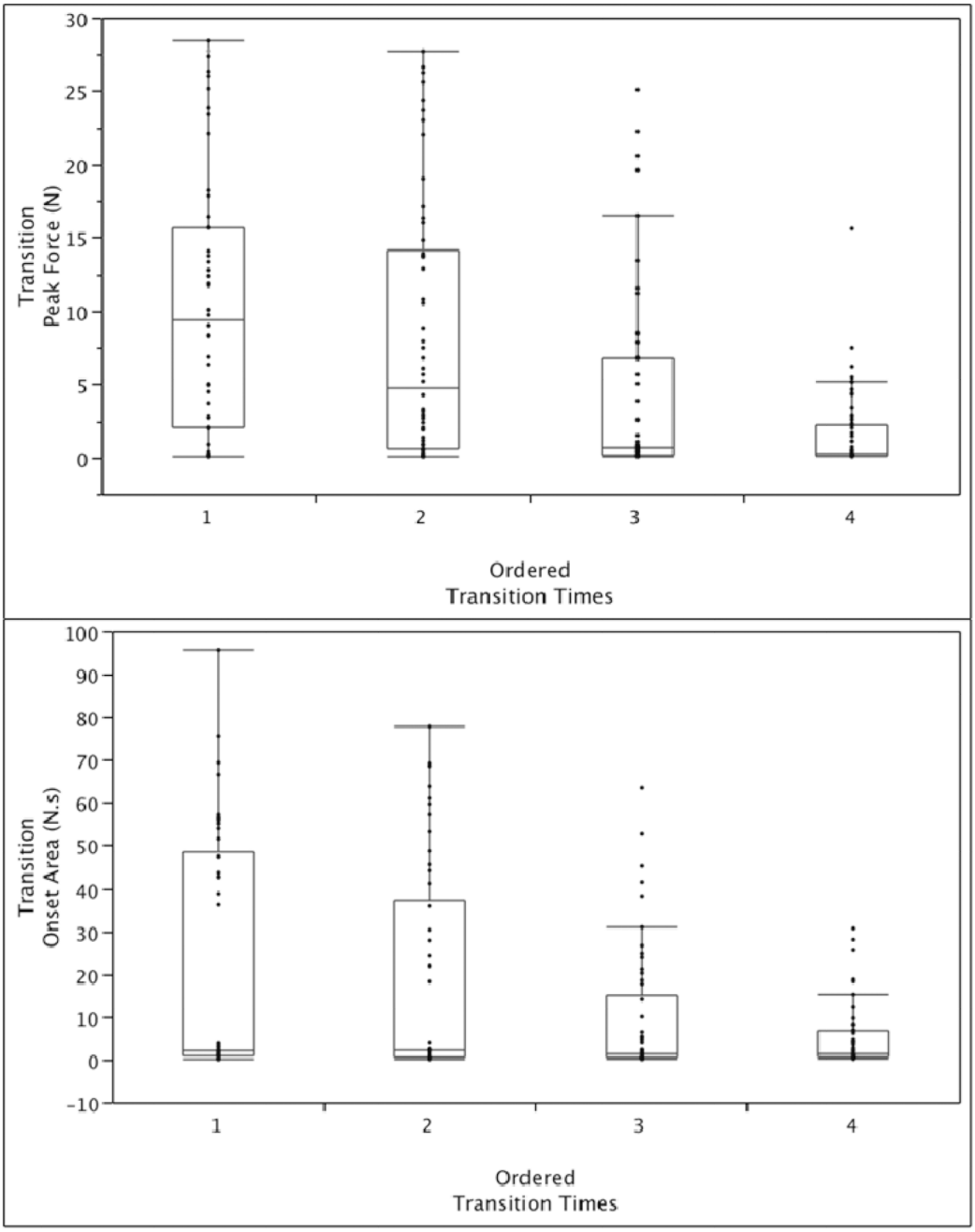

Figure 6.

The combined data from all animals are presented in box plots (median, lower and upper quartile and minimum and maximum) comparing the transition onset peak force (*top*) and area (*bottom*) across all transition times. The transition times are coded into numbers 1 through 4, with 1 being the shortest and 4 being the longest transition time tested in each respective animal. The transition onset peak force and area are smallest for the longest transition times (4), resulting in minimal to no muscle activity during the transition.

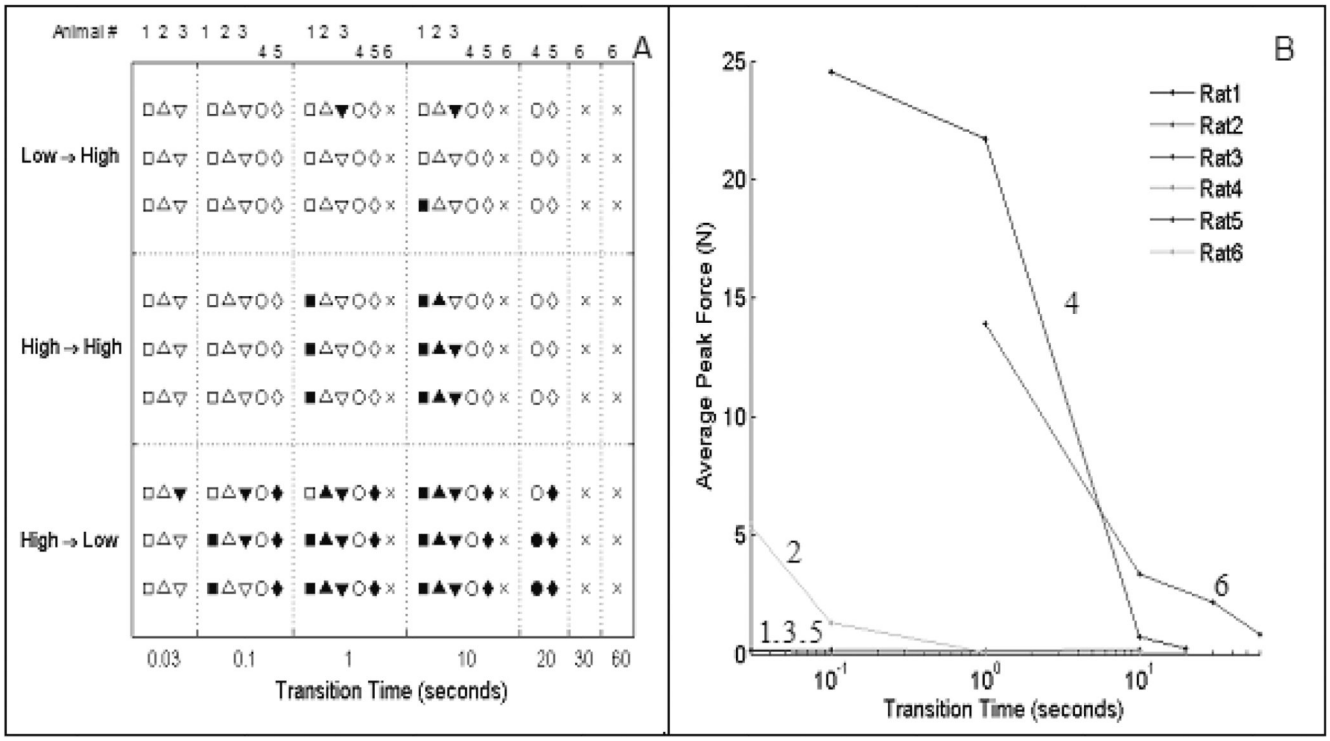

Figure 7.

7A shows all data points from the 6 randomized experiments presented as success (closed symbols) and failures (open symbols) of the frequency and amplitude transitions. Animal numbers are shown on the top and all transition times on the x-axis.

7B shows the averaged peak force data (averaged over the 3 repeats) for all animals from the "high to low" amplitude group. Animal numbers are appended next to the plots.

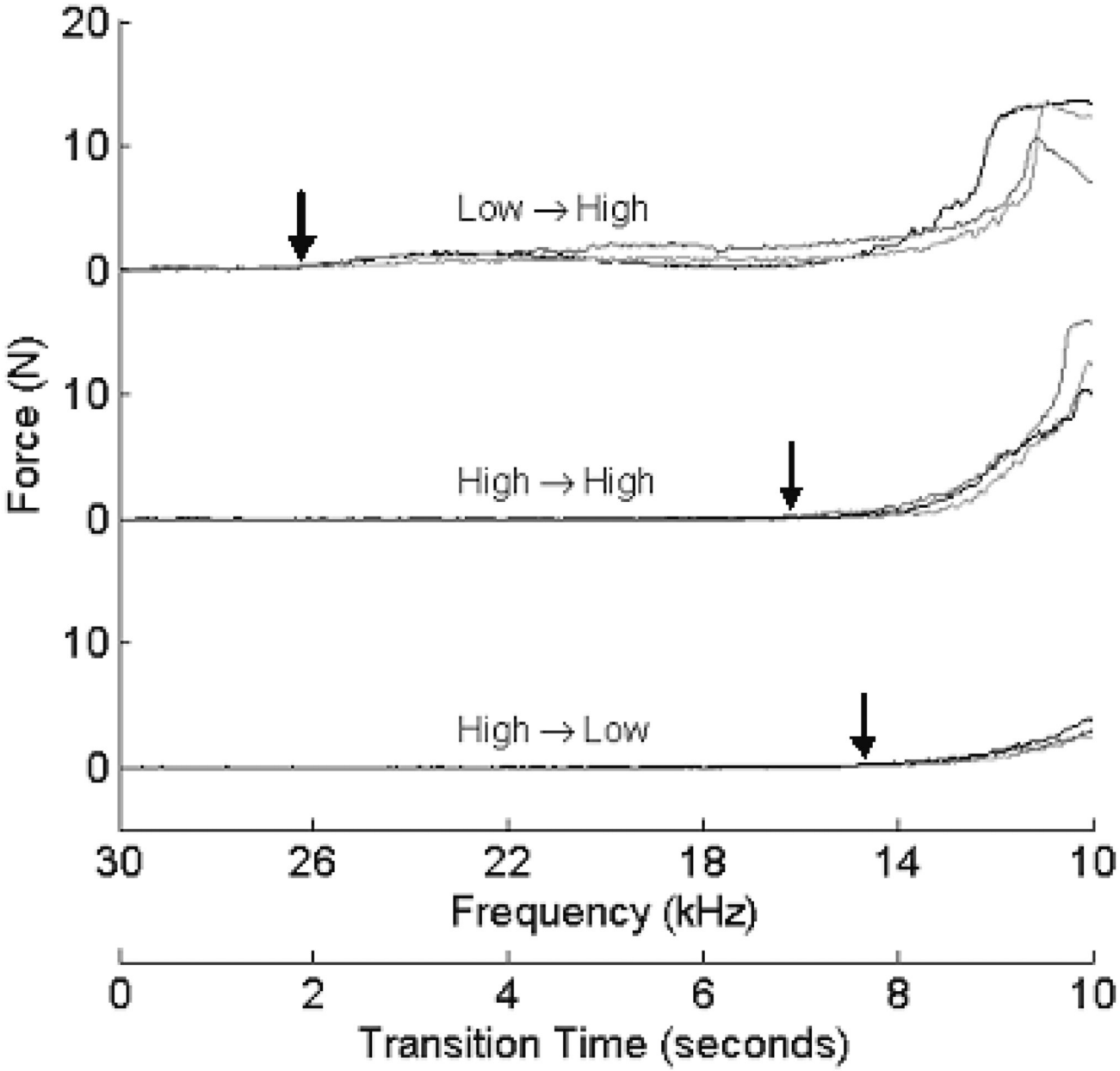

Figure 8.
Plot of transition activity during unsuccessful transitions (all at transition times of 10 s) from one animal. The transition activity starts first (earlier in time and at a higher frequency) in the “low to high “ group, followed by “high to high” and lastly in the “high to low”. This is due to the transition activity being initiated by different rates of change in the charge being delivered to the nerve.