Measurement of block thresholds in kiloHertz frequency alternating current peripheral nerve block

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Abstract

Background—Kilohertz frequency alternating currents (KHFAC) produce rapid nerve conduction block of mammalian peripheral nerve and have potential clinical applications in reducing peripheral nerve hyperactivity. The experimental investigation of KHFAC nerve block requires a robust output measure and this has proven to be the block threshold (BT), the lowest current or voltage at which the axons of interest are completely blocked. All significant literature in KHFAC nerve block, both simulations and experimental, were reviewed to determine the block threshold method that was used. The two common methods used are the High-Low method experimentally and the Binary search method for simulations.

New Method—Four methods to measure the block threshold (High-Low, High-Low-High, Binary and Random) at three frequencies (10, 20 and 30 kHz) were compared through randomized repeated experiments in the in-vivo rodent sciatic nerve-gastrocnemius model.

Results—The literature review showed that more than 50 % of publications did not measure the block threshold. The experimental results showed no statistical difference in the BT value between the four methods.

Comparison with Existing Method(s)—However, there were differences in the number of significant onset responses, depending on the method. The run time for the BT determination was the shortest for the High-Low method.

Conclusions—It is recommended that all research in electrical nerve block, including KHFAC, should include measurement of the BT. The High-Low method is recommended for most experimental situations but the Binary method could also be a viable option, especially where onset responses are minimal.

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Keywords

Electrical Nerve Block; Kilohertz Frequency Nerve Block; Block Threshold; Motor Block; Rodent; Sciatic Nerve

1. Introduction

Over the past two decades, there has been increasing interest in the use of kiloHertz frequency alternating currents (KHFAC) for the purpose of blocking action potentials in peripheral nerves [1]. KHFAC nerve block initiates a fast-acting axonal block which is rapidly and completely reversible. This type of block is a true localized conduction block of axons as opposed to a muscle fatigue or neuro-muscular junction depletion block [2]. KHFAC peripheral nerve block holds the potential for ameliorating disorders of peripheral motor, sensory and autonomic origin. It is being studied experimentally for spasticity reduction, pain control and autonomic applications e.g. cardiac disease and asthma. It is already clinically used in some recent medical applications. Enteromedics [St. Paul., MN] has developed an obesity control application, the "VBLOC" system, which uses a 5 kHz KHFAC waveform applied to the vagal nerve [3]. A 10 kHz KHFAC waveform is being applied for post-amputation neuroma pain relief [Neuros Medical, Inc., Willoughby, OH] with encouraging results [4]. Relief of back pain [Nevro Corp., Menlo Park, CA] has been obtained using a current-controlled 10 kHz waveform delivered to the thoracic spinal cord [5].

It is important to have a measure of the block *input parameters* (waveform shape, frequency, and amplitude) that determine the effectiveness of block. This is essential for comparing results of nerve block across experiments, electrodes, waveforms and nerves/axons. It is also equally important to have a robust *output measure* of successful nerve block. One measure that has been used has been termed the block threshold (BT) and is the minimum voltage or current amplitude of the KHFAC waveform at each selected frequency that results in complete block of the system under investigation [2]. Thus, this could be block of all the motor axons in a mixed nerve, a specific population of sensory axons in a nerve or even single axons where single fiber recording techniques are used.

The common method that has been used in many laboratories, including ours, to determine the BT is described below. We have named this method the "High-Low" method. The application of KHFAC typically induces an initial, brief onset response (less than one second in motor axons), a period of rapid neuronal firing, before conduction block is established [2]. The onset response is *lower for higher amplitudes and higher frequencies* of the KHFAC [2]. When the KHFAC is on for any amount of time, further increasing the amplitude produces new onset responses but decreasing the amplitude does not produce any more. This occurs because the onset is produced by a positive change in the charge delivered to the axons by the KHFAC waveform. The onset response is pronounced in motor axons. As yet, there is no dependable data on the severity of the onset response in sensory and autonomic nerves. This onset response influenced creation of the High-Low method used to measure block thresholds experimentally [2]. This method starts with test stimulation of the nerve/axon at

one end and then initiation of the KHFAC (at the selected frequency/frequencies) at a high amplitude (to minimize the onset response) [2]. Once the onset response has abated the amplitude is decreased in discrete steps until the test stimulation response is no longer blocked. The lowest amplitude where the system is completely blocked is identified as the block threshold. The amplitude step size is the resolution of the block threshold measurement.

The block threshold is also widely used for computer simulation studies of KHFAC block. Here, the common technique to determine block thresholds has been to use a Binary Search method [6]. An initial high KHFAC amplitude is selected. The choice of this amplitude is dictated by the axonal model, electrode geometry, waveform shape, frequency and other input factors and has to be determined for each particular condition. The interval from zero to this amplitude is repeatedly tested at the mid-point values with the results from one run determining the interval to test in the next run. The search ends when the pre-determined resolution of the search amplitude has been reached.

We reviewed most of the significant experimental and modeling publications on KHFAC nerve block, and tabulated the information on the block threshold (Table 1). The search criteria used to identify these publications used the terms; high frequency nerve block and kilohertz frequency nerve block but was also based on following up the citations of known electrical nerve block papers. Many papers did not mention measuring the block threshold. Usually, in these papers arbitrary amplitudes were used to show that nerve block could be obtained, but no attempts were made to map the amplitude versus frequency relationship. Some papers mentioned the block threshold but did not describe the method used to determine it. The remaining papers used one of four methods: High-Low (described above), Low-High (where the KHFAC amplitude is initiated at a low level and increased in steps or ramped up until complete block is obtained), Binary Method (described above), or Random Method (where random amplitudes are chosen over a given range).

The KHFAC onset is less with higher amplitudes and there is no new onset firing when transitioning from high amplitudes to low amplitudes. This is the key reason the High-Low method was originally developed since most of the earlier work in KHFAC nerve block was conducted on peripheral motor nerves and the method minimized the problem of the onset response. There is one concern about using the High-Low method, which is that the amplitudes tested decrease sequentially and are monotonic and could have a potential summative effect. It was unknown if this affected the determination of the true block threshold. The best way to investigate this would be to compare versus randomized amplitudes (Random method). However, a random method implies separate trials of the KHFAC at different amplitudes with each trial producing an initial onset response. The Binary method was added since it is used so commonly in simulations. A binary search has the same problem with separate trials producing onsets. However, a binary search is very efficient in finding the BT with the minimum number of trials. The Low-High method was added since it was used in three experimental papers [7-9]. However, testing a pure Low-High method would guarantee large onsets at every increasing step change in a motor system due to the positive injection of charge. Therefore, we tested it as an extension of the High-Low method as described below and named it the High-Low-High method.

The purpose of this research was to evaluate the four methods using randomized and repeated acute in-vivo experiments. The aim was to measure the error in the evaluation of the block threshold using these four methods and identify which method, if any, was superior. The methods chosen were the following; High-Low, Low-High, Binary and Random. The <u>High-Low</u> method was used as the standard method for comparison. The Low-High method was tested by using a variation of the High-Low method, which consisted of finding the BT in the High-Low method, then reducing the amplitude further down and then increasing again to measure the BT again (the <u>High-Low-High</u> method). This gave the block threshold for the Low-High method and was done to reduce the number of trials and to acquire the Low-High block thresholds without significantly larger onsets.

2.   Materials and Methods

2.1.   Surgical Procedure

Acute experiments were conducted on adult rats (Sprague-Dawley ~ 400 grams) anesthetized with inhaled Isoflurane. For each experiment an incision was made 1cm lateral to the spine, the sciatic nerve was exposed, and the superior gluteal nerve was severed. A second incision was made on the hind leg extending from the plantar surface of the foot to 1cm distal of the first incision. The sciatic nerve was exposed at its terminal branching point into the tibial, peroneal, and sural nerves, and the peroneal and sural nerves were severed. The hamstring was cut to expose the gastrocnemius-soleus muscle, which was freed from the surrounding tissue. After the Achilles tendon was cut, the tendon and gastrocnemius-soleus muscle were attached to a force transducer (Entran, Fairfield, NJ) via a customized setup. The muscle was tightened to create 1-2 N of tension and the gastrocnemius muscle was protected from drying with mineral oil. Our institutional animal care and use committee approved all animal studies.

2.2.   Electrical Stimulation and Block

A bipolar electrode was placed on the proximal sciatic nerve and was used to stimulate the nerve and generate a response in the gastrocnemius muscle (Figure 1). A second bipolar electrode was placed on the distal sciatic nerve and was used to deliver the blocking kilohertz frequency alternating current (KHFAC) waveform. Both bipolar electrodes had platinum contacts with a width of 1mm and a height of 3 mm, 2 mm spacing between contacts, and 1mm of insulation on either side of the electrode. Including the insulation, the overall electrodes have a width of 6mm and a height of 9mm. Any tissue between the cuff and the nerve was cleared in order to optimize the position of the blocking electrode and to minimize the onset response, which was characterized in Bhadra & Kilgore 2005. A distal electrode was not used in these experiments since it has previously been proven that the KHFAC block is a localized nerve block and not a neuromuscular junction fatigue block [2].

A voltage-controlled stimulator (Grass Model S88) connected to a constant current stimulus isolation unit (Grass Model PSIU6) was used to deliver stimulating pulses through the bipolar electrode proximal to the spine. Stimulation was delivered as square pulses at 1Hz with 20 μs duration [2]. The minimum amount of current needed to elicit a muscle response (activation threshold) and the minimum amount of current needed to elicit the maximum

amount of force from the muscle (saturation threshold) were mapped at the beginning of each experiment and after every set of 9 trials to monitor any change in these values. The current amplitude was set to a value 0.1-0.2 mA higher than the saturation threshold to ensure maximal activation of the gastrocnemius muscle.

A voltage-controlled waveform generator (Wavetek Model 395, Fluke, Everett, Washington) was used to deliver the KHFAC sinusoidal waveform to the distal bipolar block electrode. The three frequencies tested during the experiment were 10 kHz, 20 kHz, and 30 kHz, with amplitudes varying as described under Experimental Protocol. A 3-μF capacitor was placed in series with the output of the Wavetek generator in order to minimize direct current (DC) offsets. All noted amplitude values are the peak-to-peak voltage (V). Data were recorded using a data acquisition interface (CED Power 1401-3, CED, Cambridge, England) and Spike2 software (CED, Cambridge, England) with a sampling rate of 100 kHz. The KHFAC waveform, stimulation pulse triggers and force were recorded.

2.3. Experimental Protocol

Four different methods for determining block threshold were evaluated (Table 2). The methods are designated by names as well as numbers (for the statistical analysis). Method 1 was the High-Low method, which was similar to that used by Bhadra and Kilgore 2005. A step size of −1 V was used and the block threshold was determined to be the lowest value at which complete block was achieved and no muscle twitches were recorded. For most trials, the starting amplitude was 10V (34 of 36 trials). Rarely complete block was not achieved at that amplitude and a higher value of 16V was used as the starting amplitude (2 of 36 trials). Method 2 was the High-Low-High method, which is similar to Method 1 where the starting block was a suprathreshold value (also 10V or 16V). Block threshold was determined after decreasing KHFAC amplitude two V past block threshold, and then increasing the amplitude again in one V steps. Since a block threshold using Method 1 could be determined in the process of conducting Method 2, these two methods were combined and evaluated within the same trial. Method 3 was the Binary method used to explore a range of values within the range of 0-16V. Method 4 was the Random method. The amplitude ranges for the random search were selected for each frequency and were based on a preliminary experiment. Lower and upper amplitudes were determined for the three frequencies using non-randomized experiments to find the amplitude range which would definitely include the BT (BT amplitude range shown in Table 2, last three lines).

The KHFAC was applied five seconds after the initiation of proximal stimulation. Each KHFAC application was maintained until the onset response disappeared, and block could be correctly evaluated. This determination was an interactive process and therefore these times varied with each trial. Each step was maintained for approximately 4 to 10 seconds with 3 to 10 seconds before the next KHFAC amplitude was tested.

Three sets of randomized trials were conducted for each animal. Each set included the four different blocking threshold methods at frequencies of 10 kHz, 20 kHz, and 30 kHz. Since Methods 1 and 2 were evaluated within a single trial, this resulted in 9 trials per set and a total of 27 trials per animal. Each trial started and ended with proximal electrode stimulation alone. The conduction block was initiated approximately 5 seconds after proximal

stimulation and was left on for varying times depending on the block threshold method being tested (average 30.7 seconds, standard deviation 17.85). For Methods 1 and 2 the Wavetek output was not turned off between each block value tested, whereas for Methods 3 and 4 the Wavetek output was turned off for 1-2 seconds in between each block value. A two-minute wait was used in between each trial.

Block threshold data was collected from a total of five animals. The first animal was a preliminary experiment, and the results were used to determine the range of amplitudes tested for the random trials. The preliminary experiment data was not included in the final data analysis since the protocol for all following experiments was modified to include Method 4. The bipolar electrodes were cleaned between experiments using an ultrasonic bath.

2.4. Data Analysis

Digitized data sets were processed using commercial software (MATLAB, Math Works, Natick, MA) to derive the required data variables. Extracted data were analyzed using a commercial statistical software package (JMP, SAS Institute, Cary, NC). 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, to determine the influence of each of the independent parameters as well as interactions between the parameters on the response variables. The control variables were: animal number, trial number, set number, frequency, and method number. The output variables were: the determined block threshold from each trial, the sum of the onset responses in each trial (area under the curve in Newton.seconds), and the time taken to determine the block threshold from the start of the first KHFAC application. A one way analysis of variance (ANOVA) and post-hoc Tukey Kramer HSD (honestly significant difference) tests were used to analyze the collected block threshold data. Three separate Tukey Kramer HSD tests were used to evaluate the block threshold against method type, set number, and KHFAC frequencies. These tests compare all possible pairs and were utilized to determine which group or groups were significantly different.

3. Results

3.1. Complete Motor Block

A complete and reversible motor block was achieved in all trials performed for all frequencies tested. In all animals tested, block thresholds were successfully determined using each method. The block threshold values ranged from 3 V to 13 V. Figure 2 displays an example of trials conducted for each block threshold method tested. For the binary and random method trials, the Wavetek output was turned off between the different amplitudes tested. Pulses from proximal stimulation can therefore be seen prior to block onset. In this example, the High-Low was able to determine the block threshold in the least amount of time, followed by Method 2, Method 3, and finally Method 4, which took the longest. Randomization was tested primarily to evaluate if there was a time or order bias within the other thresholding methods. These examples (Figure 2) were taken from the same experiment, and each method resulted in the same block threshold (6 V).

3.2. Block Threshold Method Comparison

An ANOVA effects test resulted in a p-value of 0.4024 for the block threshold methods, indicating that there was no significant difference in the measured block thresholds between the four methods tested. This is also shown in Figure 3 with the Tukey-Kramer test. Also, no significant differences were found between the three sets of trials performed for each rat, which is shown in Figure 4. This indicates that there was no significant change in the block threshold over the duration of the experiments. However, the Tukey Kramer HSD test does show a significant difference between the block thresholds determined at all KHFAC frequencies (10, 20, and 30 kHz), as is expected. Figure 5 shows that higher KHFAC frequencies require higher block amplitudes in order to achieve a complete block.

The onset area during each trial was analyzed for the four methods and is shown in Figure 6. The results are as follows. The High-Low method had a mean of 9.48 N.s with a standard deviation of 20.48 and a range of 0.13 to 93.1 N.s. The High-Low-High method had a mean of 11.48 N.s with a standard deviation of 21.44 and a range of 0.13 to 93.8 N.s. The Binary method had a mean of 48.41 N.s with a standard deviation of 50.6 and a range of 5.58 to 190.78 N.s. The Random method had a mean of 49.19 N.s with a standard deviation of 57.91 and a range of 2.89 to 227.42 N.s. An ANOVA effects test resulted in a p-value of <0.0001 for the BT method indicating significant differences in the total onset area between the four methods.

The time needed to determine the BT was also analyzed for every trial (Figure 6). The results are as follows. The High-Low method had a mean of 30.72 s with a standard deviation of 17.84 and a range of 10 to 83 s. The High-Low-High method had a mean of 57.33 s with a standard deviation of 23.3 and a range of 35 to 120 s. The Binary method had a mean of 89.91 s with a standard deviation of 44.78 and a range of 40 to 200 s. The Random method had a mean of 168.44 s with a standard deviation of 85.76 and a range of 70 to 420 s. An ANOVA effects test resulted in a p-value of <0.0001 for the BT method indicating significant differences in the time to determine the BT between the four methods.

4. Discussion

These experiments successfully tested four methods of determining the KHFAC block threshold in complete block of the motor component of the rat sciatic nerve. Complete motor block was obtained for all trials at all the three tested frequencies. The statistics of the data from the repeated, randomized trials showed that there were no differences between the four methods tested in determining the block threshold at a resolution of 1 V_{pp}. There were also no differences in the set number thus confirming that the position of the trial chronologically in the experiment did not affect the block threshold determination. As expected, the block thresholds were statistically different for the three frequencies tested. The onset area and time to determine BT was similar for the High-Low and High-Low-High methods and significantly higher for the Binary and Random methods.

Recently it has been shown that KHFAC nerve block has a carryover effect where the nerve block can persist even after the KHFAC has been turned on [10]. However, this effect appears after a minimum KHFAC application time of 15 minutes. The average duration of

KHFAC application for the block threshold testing in the present research was 30.72 seconds (High-Low method) to 168.44 seconds (Random method) and the range of durations for all methods was 10 seconds to 420 seconds. Therefore, it is very unlikely that the carryover block effect would have any influence on the block threshold measurements.

Our recommendations for choosing a method to measure block thresholds are based on four parameters. These are; any differences in the BT between methods, onset area, time to measure the BT, and the system being studied (motor, sensory, autonomic or mixed). This study shows no differences between methods. The onset is lowest for the High-Low method (Method 1) and for the High-Low-High method (Method 2). It should be noted that if a pure Low-High method was used as opposed to our choice of a High-Low-High method, the onsets would be as severe as for the random method, with onsets at every increasing step. Similarly, the time to measure the BT was shortest for the High-Low method and slightly longer for the High-Low-High method.

Based on these findings, we believe that the High-Low method (Method 1) is most appropriate for determining KHFAC block thresholds of motor and autonomic motor systems. The method minimizes the onset response yet is efficient in determining the block threshold rapidly (in less than ~ 90 seconds). However, if there is need for the resolution of the block threshold amplitude to be finer, then it does imply much longer trials. The Low-High method (Method 2) does not grant any extra advantages compared to Method 1 and is not recommended. The binary search method (Method 3) is very efficient for this requirement as the resolution can be increased with the addition of a small number of extra trials. However, the binary search method will induce an onset response if used to determine block thresholds for motor systems. There is some indication that suggests that the onset response may be smaller in pure sensory systems and the binary search method may be appropriate (unpublished data). The Random search method (Method 4) is not recommended, due to both larger onsets and longer time to detect the BT, unless the requirements for statistical power in the experiment dictate it.

The literature review shows how common it has been to not measure the block threshold. Experimentally more than 50% of publications did not measure the KHFAC block thresholds. We advocate that all research in electrical nerve block should include a paradigm to rigorously evaluate and measure block thresholds. This will allow relevant comparisons within and between experiments, interventions and across laboratories. We suggest the usage of the High-Low method for most determinations but the binary method could also be a viable option.

Acknowledgements

ABBREVIATIONS:

KHFAC	Kilohertz Frequency Alternating Current
BT	Block Threshold

V   Vpp = Peak to Peak voltage

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HIGHLIGHTS

- A literature review showed 50% of papers on electrical nerve block did not measure block thresholds.

- Four block threshold measurement methods were evaluated using randomized in-vivo experiments.

- There were no statistical differences between the four methods.

- The High-Low method is recommended as the most efficient way to measure the block threshold.
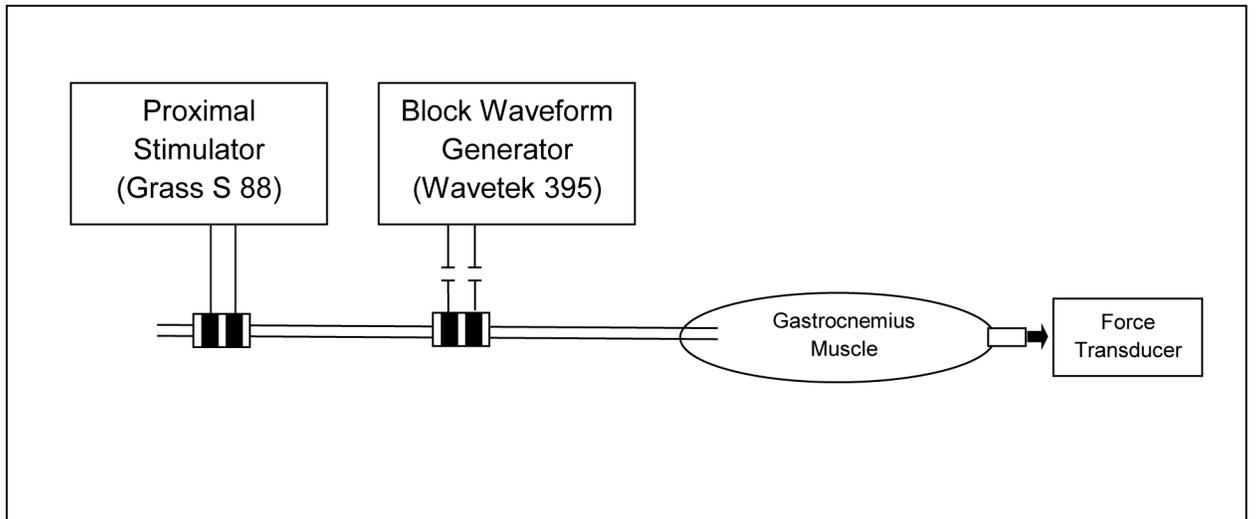
Figure 1:
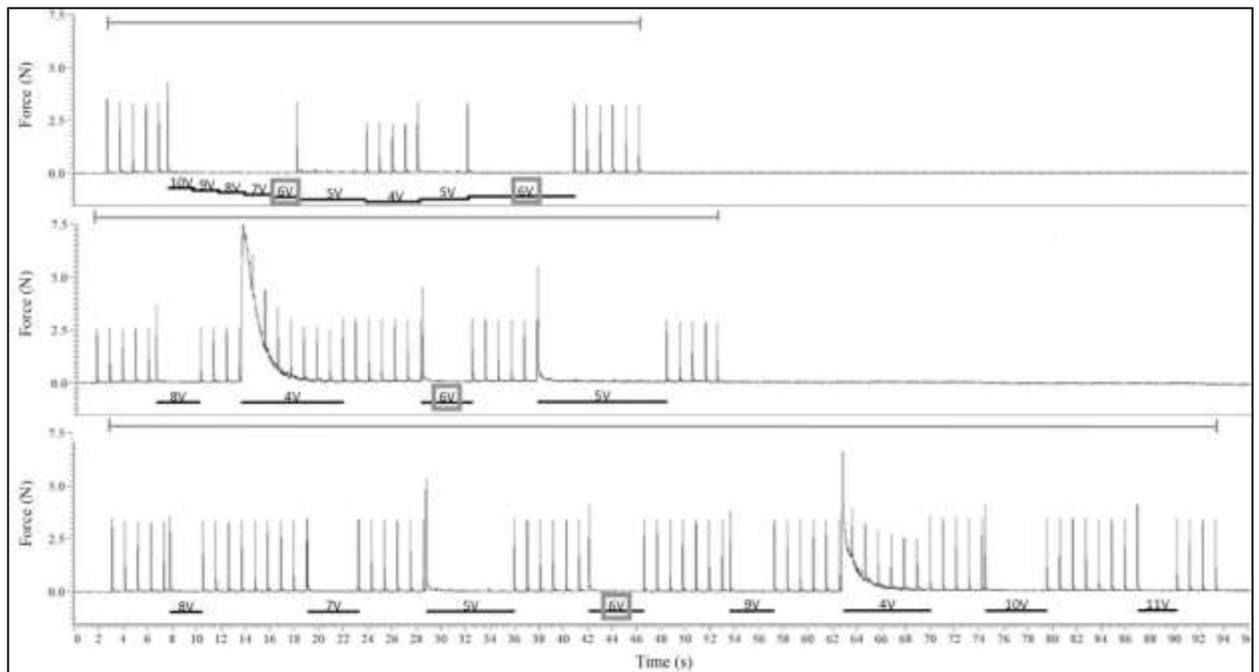In-vivo setup for testing KHFAC nerve block thresholds.

Figure 2:

Example of three trials evaluating four different block threshold methods. Force is shown in Newtons. All these three trials evaluated a 20 kHz KHFAC blocking waveform. The top graph displays a typical trial for Methods 1 (High-Low) and 3 (High-Low-High). The blocking waveform is initiated at 10 V to determine block threshold using the High-Low Method, and then once block threshold is passed the blocking amplitude is lowered by 2 V and then increased again and block threshold is re-determined through the High-Low-High Method. The middle graph displays a typical trial for Method 2, the Binary Method. Blocking amplitude begins at 8 V. The bottom graph displays a typical trial for Method 4, the Random Method. The gray bars above each graph indicate when proximal stimulation was being delivered. The black bars below each graph and accompanying text indicate the duration and amplitude of the block. A gray box shows the determined block threshold, 6 V for all cases in this example.
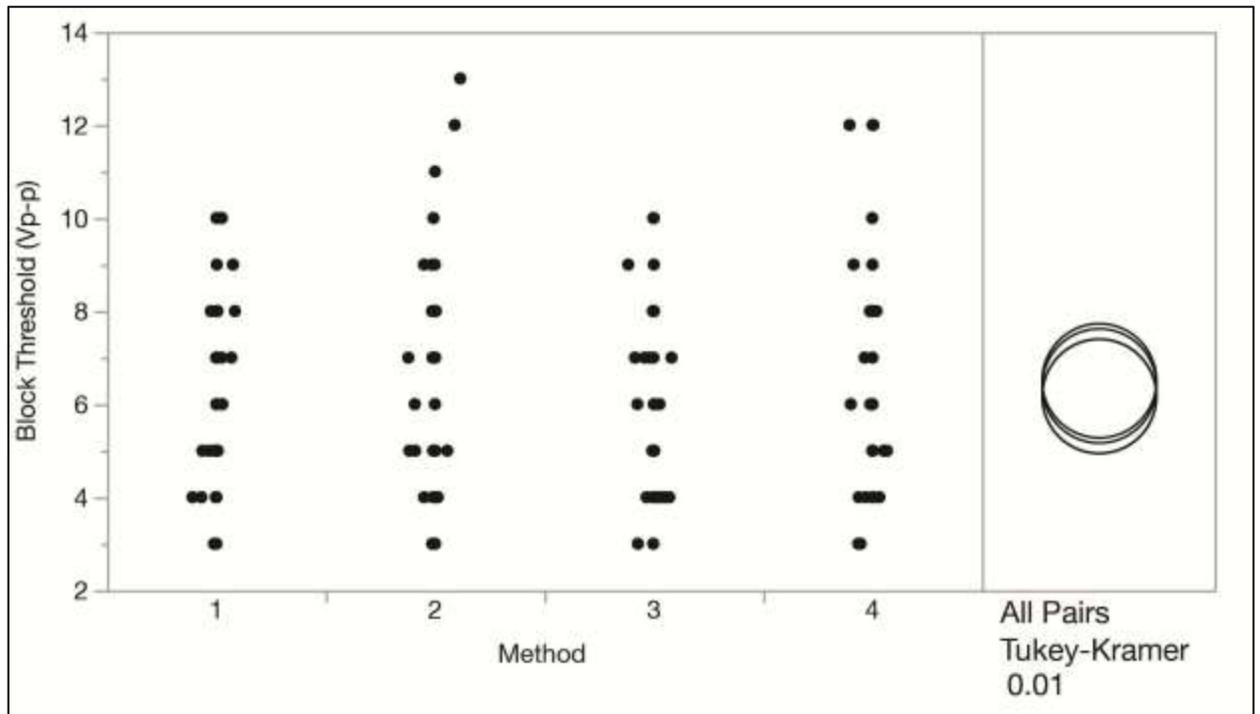
Figure 3:
Block threshold versus method with the Tukey Kramer HSD Test. Block thresholds from all trials conducted on four animals (N = 108) are plotted. The overlap between the circles in the All Pairs test shows that there is no significant difference between the group means for all possible pairs of method types at $\alpha = 0.01$.
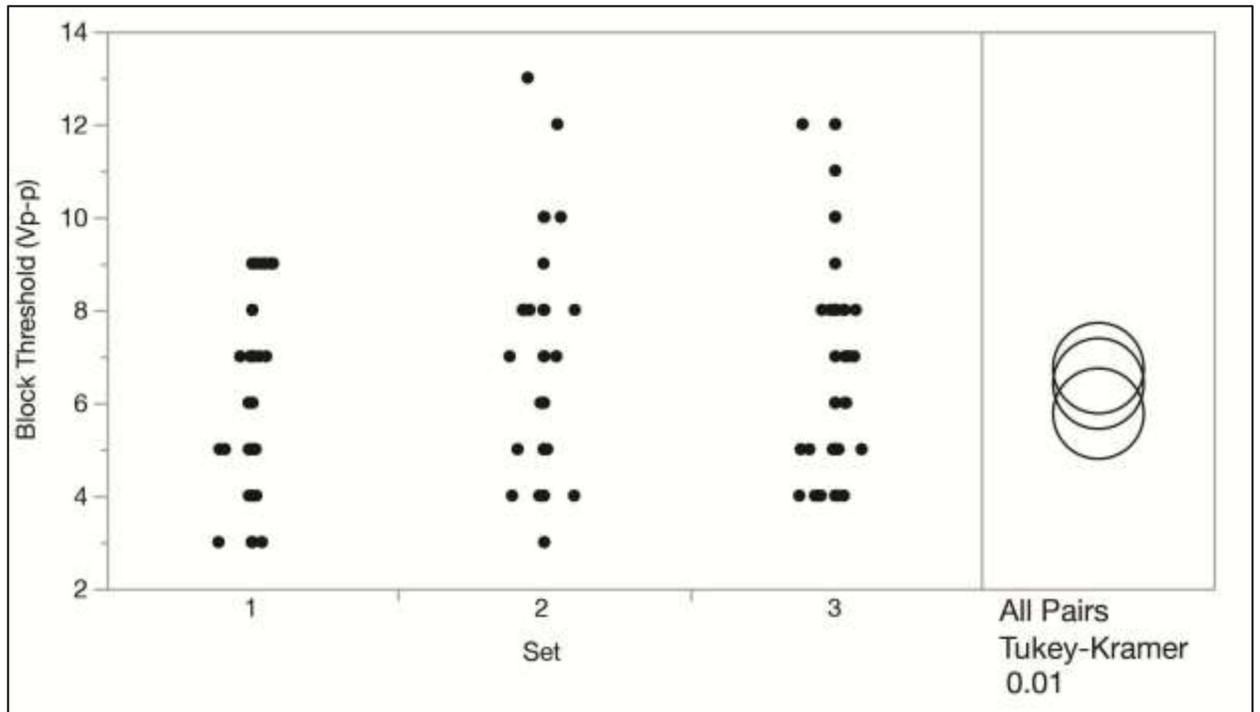
Figure 4:
Block threshold versus set number with the Tukey Kramer HSD Test. The All Pairs test shows that there is no significant difference between the groups. Block thresholds are comparable over the time of the acute experiments at $\alpha = 0.01$.
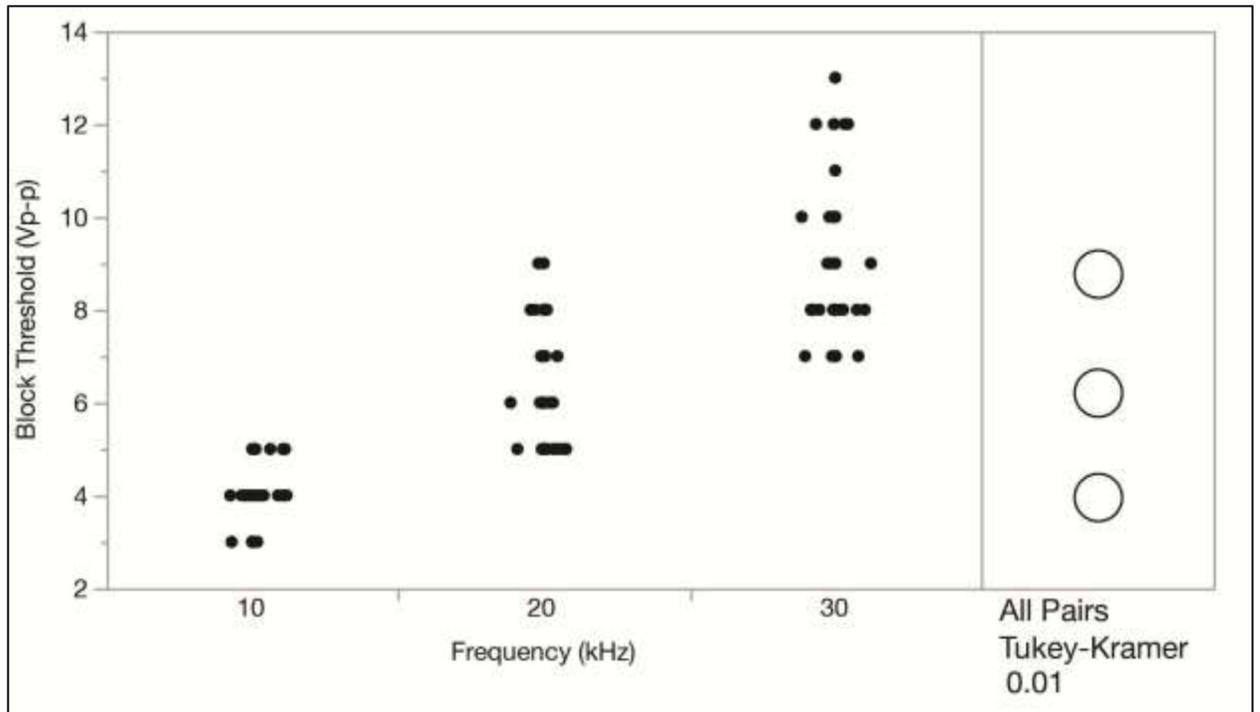
Figure 5:
Block threshold versus KHFAC frequency with the Tukey Kramer HSD Test indicates that there is a significant difference between the group means for all possible pairs of KHFAC frequencies at $\alpha = 0.01$.

Figure 6:
Onset area and trial time needed to measure the BT versus the four methods.

Table 1:

A summary of block threshold information from simulation and experimental publications on KHFAC nerve block. The underlined numbers indicate the highest incidences.

Block Threshold Information in the publication	Simulation publications Total = 14		Experimental publications Total = 44	
	# out of 14	References	# out of 44	References
Not measured	2 of 14	[11, 12]	23 of 44	[3, 5, 11, 13-31]
Mentioned but method was not described	7 of 14	[32-38]	6 of 44	[12, 39-43]
Method : High-Low	1 of 14	[44]	11 of 44	[2, 9, 45-53]
Method : Binary Search	4 of 14	[6, 53-55]	0 of 44	
Method : Random Search	0 of 14		1 of 44	[56]
Method : Low-High	1 of 14	[44]	3 of 44	[7-9]

Table 2:

Summary of experimental procedure for the four methods

Method Number	Method Name	Description All voltages are peak to peak
1	High-Low	Start block suprathreshold at 10 V or 16 V. Decrease in 1 V decrements until twitches return.
2	High-Low-High	Start block suprathreshold at 10 V or 16 V. Decrease in 1V increments until twitches return. Continue to decrease until 2 V below first threshold. Increase in 1 V increments until twitches disappear
3	Binary	Search a range from 0-16V starting in the middle at 8V. Two possible next steps: 1) If complete block achieved then values above 8V eliminated and test middle of remaining range, from 4V. 2) If complete block was not achieved, then values below 8 V eliminated and test middle of remaining range, or from 12V. Repeat steps 1 and 2 until block threshold is determined within a 1V resolution
4	Random	Test block values in a randomly generated order within the below ranges (ranges based on preliminary data from animal # 1): 10 kHz: 2-9 V 20 kHz: 4-11 V 30 kHz: 5-12 V