ELECTRICAL CONDUCTION BLOCK IN LARGE NERVES: HIGH-FREQUENCY CURRENT DELIVERY IN THE NONHUMAN PRIMATE

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ABSTRACT: Recent studies have made significant progress toward the clinical implementation of high-frequency conduction block (HFB) of peripheral nerves. However, these studies were performed in small nerves, and questions remain regarding the nature of HFB in large-diameter nerves. This study in nonhuman primates shows reliable conduction block in large-diameter nerves (up to 4.1 mm) with relatively low-threshold current amplitude and only moderate nerve discharge prior to the onset of block.

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The delivery of high-frequency alternating current (HFAC) to peripheral nerves can produce a reversible conduction block.[1] There is considerable hope that the method may be useful for the clinical treatment of disorders associated with pathological neural activity, such as spasticity or peripherally triggered pain. HFAC delivery has been the focus of several recent studies, which have pursued an optimal waveform for delivery, optimal electrode design, and a biophysical understanding of the mechanisms of this type of nerve conduction block. The results of these studies demonstrate that high-frequency block (HFB) can be established quickly ($\leq$1 s to several seconds)[2,3] and reversed quickly ($\leq$1 s).[2] The induction of HFB requires the use of a frequency that is at least $\backsim$2 kHz[4–7] and a waveform amplitude that is typically 3–10 V (1–10 mA for current-controlled studies) across preparations.[4,6–9] The minimal waveform amplitude required to induce HFB, the block threshold, is dependent on the waveform frequency[4,6,8,10,11] and geometry of the blocking electrode.[12] When HFAC is first applied to a nerve, it produces an intense volley of activity in the target nerve, the "onset response," before inducing block. The magnitude and duration of this onset response are also functions of the waveform frequency,[6,10] waveform amplitude,[1,6,10,13,14] and electrode geometry.[14] HFB has been successfully demonstrated in a chronic electrode preparation in the cat[6] and likely results, mechanistically, from depolarization-induced inactivation of sodium channels.[15]

The aforementioned recent studies have made significant progress toward the clinical implementation of HFB, particularly for myelinated fibers. However, they were performed in small nerves in the sea slug, frog, rat, and cat. It is not clear whether HFB can be achieved in large-diameter nerves using similar waveform amplitudes and frequencies, and whether the onset response will be similar to that observed in small nerves. In this study we investigate the application of HFB to the large-diameter median nerve in the monkey.

METHODS

Experiments were performed in a total of three nerves in two adult male nonhuman primates (*Macaca fascicularis* and *Macaca mulatta*). After induction of anesthesia with 10 mg/kg ketamine, each monkey was intubated, and sedation was maintained with 2% isoflurane. Blood pressure, heart rate, respiratory rate, and body temperature were monitored throughout the experiments and remained in the normal range. All animal care and surgical and research procedures were consistent with the *Guide for the Care and Use of Laboratory Animals* and were approved by the Institutional Animal Care and Use Committee of Northwestern University.

The left median nerve of the *M. fascicularis* (diameter 3.0 mm), and the left and right median nerves of the *M. mulatta* (diameters 3.9 and 4.1 mm, respectively) were evaluated. For each of the three nerve preparations, two 10–15-mm sections of nerve were dissected free of surrounding tissue, and two nerve cuff electrodes were placed around the exposed nerve. Both electrodes were made of silicone rubber with platinum contacts. The contacts were 9-mm $\times$ 1-mm rectangles with 2.5-mm intercontact spacing.[12] The proximal electrode was either bipolar or tripolar and was used to deliver 1.0-Hz supramaximal test stimuli (single

Abbreviations: ANOVA, analysis of variance; HFAC, high-frequency
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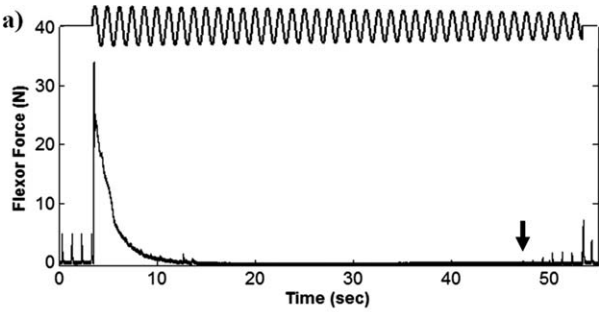
monophasic pulses, 2.0 mA, 50–300 μs). The distal electrode was bipolar and was used to deliver a 10-, 20-, 30-, or 40-kHz voltage-controlled (*M. fascicularis*) or current-controlled (*M. mulatta*) sinusoidal blocking waveform.[6,10] Each of the four fingers was tethered to a single series-loaded force transducer to monitor finger flexor force.

The block threshold and degree of onset response contraction (at threshold amplitude) were assessed at each frequency using previously established block-randomized protocols (three repeats/frequency/nerve for block thresholds and six repeats/frequency/nerve for onset response).[10,12,14] The degree of onset response was quantified by integrating the flexor force over the first 5 s of approximately 6 s of HFAC delivery (a period of 6 s was used to minimize the effect of preparation fatigue on the onset response).

RESULTS

HFAC delivery at frequencies of 20 kHz and higher resulted in a complete and reversible conduction block in each of the three median nerves tested. HFAC delivery at 10 kHz resulted in tetanic contraction in each nerve. Twenty-kilohertz stimulation resulted in a long-duration ($\backsim$30 s) onset response for the 3.9-mm nerve. This frequency was not repeatedly evaluated for block threshold in this nerve to prevent muscle fatigue.

Figure 1a shows finger flexor force during a block threshold trial on the 3.9-mm nerve at a frequency of 30 kHz in which amplitude was decremented 0.1 V/s to determine the minimum blocking amplitude. The initial onset response contraction lasted approximately 10 s. The absence of twitches during HFAC delivery indicated complete conduction block of the flexor motor axon pool. Figure 1b summarizes the results of the randomized block threshold and onset response trials for each of the three nerves. Block threshold values for the *M. mulatta* monkey have been converted to voltage values (although constant-current delivery was used) to allow for direct comparison with the *M. fascicularis* data. Values were converted using the measured blocking electrode impedance of $\backsim$500 Ω for frequencies in the range tested. The table portion of Figure 1 shows that block threshold correlated positively with nerve diameter. Larger nerves required higher amplitudes to induce HFB. Mean block thresholds increased with waveform frequency for each nerve tested, and the mean onset response integral showed a decreasing trend with frequency for each nerve. The effects of nerve diameter and frequency on block threshold were both found to be significant using analysis of variance (ANOVA) at the $\alpha = 0.05$ level. The effect of nerve diameter on the integral of the onset



b)

Nerve	Nerve Diam. (mm)	Freq. (kHz)	Block Thresh. Mean±Stdev (V)	Onset Integral Mean± Stdev (N·sec)
m. fasc. Left	3.0	20	2.23±0.15	12.7±1.4
		30	3.2±0.2	8.9±1.8
		40	4.27±0.06	6.0±1.0
m. mulatta Left	3.9	20	Not Tested	75.0±10.3
		30	4.83±0.92	67.4±5.1
		40	7.94±0.64	66.7±8.6
m. mulatta Right	4.1	20	6.89±0.24	Not Tested
		30	10.15±0.34	Not Tested
		40	Insuff. Amp.	Not Tested

FIGURE 1. (a) Finger flexor force during HFAC block threshold trial on the left median nerve in the *M. mulatta* monkey at a frequency of 30 kHz. Relative HFAC amplitude is indicated diagrammatically. HFAC amplitude started at 15.0 V, and threshold was measured to be 10.6 V (the arrow indicates the first twitch resulting from partial conduction block). **(b)** Table summarizing the results of the randomized block threshold and onset response trials for each of the three nerves tested. The waveform generator was unable to generate sufficient amplitude to produce a complete conduction block at 40 kHz for the 4.1-mm nerve.

response was also significant using ANOVA at the $\alpha = 0.05$ level, but the effect of frequency was not significant. Muscle twitch force recovered to a pre-HFAC amplitude, typically 30–120 s, after cessation of blocking current delivery.

DISCUSSION

This study has demonstrated that robust and reversible HFB is possible in large-diameter nerves. Block thresholds were in the range of 2–10 V for a frequency range of 20–40 kHz, which is slightly larger than the amplitude range reported for the 1-mm-diameter rat sciatic nerve in this frequency range.[10] Our findings show a positive correlation between nerve diameter and block threshold for the three nerves tested, a trend that has been suggested in simulation studies.[12,15] Electrode geometry has previously been shown to substantially impact onset response.[14] The difference in magnitude of onset response shown between the 3.0- and 3.9-mm nerves may be explained by an incomplete circumferential coverage of the nerve in the experiment on the 3.9-mm nerve. The onset response in the three nerves was similar in its rate of decay to that observed in other species for cases in which electrode geometries were not optimized

for minimizing onset firing.[14]

This study has demonstrated HFB in nonhuman primates and is an important step toward the clinical implementation of HFB. It shows that block can be reliably achieved in large-diameter nerves (up to 4.1 mm) with moderate threshold amplitudes and moderate onset response firing. Our findings also suggest that human trials of HFAC would likely result in the desired HFB. However, more work is required to produce an electrical blockade without significant onset response.[16,17] Elimination of the onset response will be important for some applications.

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