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Current-Distance Relationships for Peripheral Nerve Stimulation Localization

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BACKGROUND: Successful peripheral nerve blocks require accurate placement of the injection needle tip before local anesthetic application. In this investigation, we experimentally reconstructed polarity-dependent (anode and cathode) stimulation maps using ex vivo and in vivo animal models.

METHODS: A novel ex vivo configuration (muscle–nerve composite) was first used to probe both cathodic and anodic stimulation characteristics. The electrophysiology (compound nerve action potential, CAP) of rat sciatic nerve was recorded at varying stimulation (monopolar electrode) distances and intensities. We repeated this methodology with an open dissection rat model that was more analogous to the clinical setting. Resultant data from the current sweeps were plotted as a 3-dimensional distance–stimulus–CAP map. These plots depict the minimum stimulation currents required for nerve activation and describe the expected electrophysiological outcomes as a function of distance and input stimulus intensity. The stimulation maps provide positional information relevant to clinical procedures such as nerve localization during regional anesthesia.

RESULTS: Cathodic stimulation produced a complex biphasic electrophysiological response. The CAP amplitude (with fixed current) increased as the electrode moved closer towards the nerve, but decreased upon close proximity or nerve contact. This phenomenon was dependent upon stimulation intensity and was observed in both ex vivo and in vivo models. Anodic stimulation produced a monotonic relationship, with the CAP increasing with closer electrode-to-nerve distances. Minimum extraneural activation thresholds were found to be 0.34 ± 0.11 mA (mean ± SD) and 0.63 ± 0.12 mA for cathode and anode stimulation, respectively. Intraneural thresholds were substantially lower, 0.12 ± 0.03 mA and 0.32 ± 0.09 mA, for cathode and anode, respectively.

CONCLUSION: Cathodic stimulation may produce conduction block at close tip-to-nerve distances. In contrast, anodic stimulation elicited output characteristics that were predictable and more suitable for nerve localization. We believe anodic stimulation is a viable option at near-nerve distances, despite the increased current requirements. This hypothesis is a paradigm shift in stimulation nerve localization, which conventionally has been cathode based. The hypothesis should be clinically validated. (Anesth Analg 2011;112:236–41)

Successful peripheral nerve blocks require accurate placement of the injection needle tip before anesthetic application. Originally, anatomical landmarks and patient feedback to needle–nerve contact were used as guidance cues for needle positioning, but patient variability (especially in developing children or in deep body nerves), discomfort, and the potential for nerve injury complicated outcomes.[1,2] About 25 years ago, nerve stimulation began to gain widespread adoption as an objective aid to nerve localization. Although stimulation-guided nerve localization was an improvement over the prior approaches, the risk of nerve puncture with the stimulating electrode was not eliminated.[3] Intraneural injection of anesthetic may lead to inflammation or neurologic deficits,[4–6] whereas inaccurate localization may result in poor block quality. Ultrasound imaging has been used to provide anatomic visualization in assisting peripheral nerve blocks. However, stimulation-based techniques remain a viable asset, especially in cases of myopathies, edema, or subcutaneous emphysema in which ultrasound imaging may be compromised.[7–9]

There is uncertainty regarding the current–distance relationships and the limit of safe current intensities.[10] Previously, 0.5 milliamp (mA) was regarded as an appropriate procedural end point.[11,12] Other acceptable amplitudes include 0.2 mA and 0.1 to 0.5 mA, although such low intensities risk intraneural placement.[5,13] These current ranges are applicable only for close nerve-to-tip proximities. Away from the nerve, the landscape is not well characterized. Computational models that predict current–distance relationships have thus been used as a supplementary analysis tool.[14–16] However, these mathematical formulations have minimal experimental validation. In this study, our goals were 2-fold: (i) to verify unique stimulation properties put forth by mathematical models (cathode block phenomenon, polarity-dependent stimulation thresholds) and (ii) to develop current–distance maps that integrate compound action potential (CAP) amplitudes. These objectives were performed using novel experimental preparations involving extracted nerve–muscle composites (ex vivo) and an open dissection mode (in vivo).

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METHODS

Ex Vivo Sciatic Nerve-Muscle Preparation

The experimental protocol was approved by the Purdue University Animal Care and Use Committee, and the procedures may be found in previous publications.[17] Male Sprague Dawley rats weighing 350 to 425 g were used in this study. Animals were first anesthetized with 80 mg/kg ketamine and 10 mg/kg xylazine and the entire sciatic nerve extracted (~4 cm length). The nerve was placed in a cold oxygenated Krebs solution for 1 hour before experimental testing. A piece of muscle harvested from the hamstring was also removed (18 mm × 10 mm × 5 mm). The muscle was blotted to remove excess body fluid and the nerve–muscle composite was loaded into a modified sucrose gap chamber (Fig. 1A; details of the experimental chamber and its various incarnations may be found elsewhere[18,19]). The muscle sample was placed into the central well and the sciatic nerve set into a slit that was cut in the musculature. Silicone grease and plastic cover slips were used to isolate the nerve between the different fluid wells. The ends of the nerve were bathed in isotonic KCl. Custom-made Ag/AgCl wires were used as the stimulating and recording electrodes. The stimulating electrode (0.5 mm diameter) was insulated with a rubber coating and polished to have a sharp conical tip (30° taper). Conductive tip length was 0.5 mm to approximate a point source. For all electrophysiology, a constant current source (Cygnus SIU90, Delaware Water Gap, PA) was used in conjunction with a Neurodata stimulator (Neurodata PG4000, New York, NY) to deliver 100 μs square current pulses[20,21] at 0.33 Hz. The shape, polarity, duration, and magnitude of the constant current source were verified with an oscilloscope (Tektronics TDS 210 < Beaverton, OR). Neural recordings were made with a Neurocorder amplifier interfaced to custom LabVIEW (National Instruments) software.

Constant Current Sweeps

A fixed current protocol was used to chart the current–distance relationship for nerve stimulation. Briefly, the constant current source was first set to a low current level (i.e., 0.5 mA) and placed on the nerve centerline (0 mm position). The stimulating electrode was then moved to distances of 2, 4, 6, and 8 mm away from the nerve, while simultaneously recording the electrophysiology at each step. This cycle was repeated up to a current of 5.0 mA at 0.5-mA increments for both the cathode and anode regimes (Fig. 1C). For each fixed level "current sweep," the CAP magnitudes were normalized to the respective peak CAP. A normalized CAP of 1.0 denoted the maximum CAP for that stimulation condition.

Direct Contact Nerve Activation

To elucidate conduction characteristics upon electrode–nerve contact, we conducted a second protocol with the ex vivo preparation. In this configuration, the stimulating electrode was positioned on the nerve centerline (0 mm). The electrophysiology was then recorded at cathodic current levels ranging from 0.0 to 2.0 mA (0.25 mA step sizes). The experiment was repeated with the anode connection. Individual CAP values were normalized to the maximum CAP found for each polarity condition.

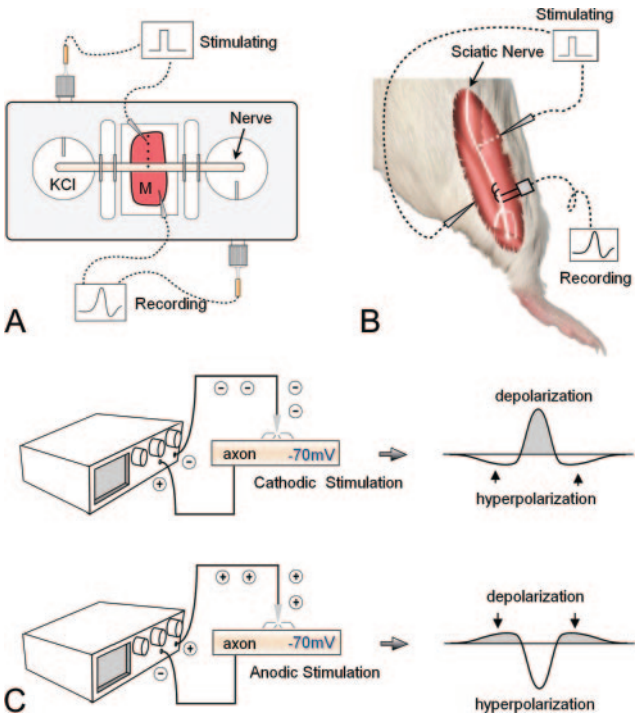

Figure 1. A, Ex vivo electrophysiological setup (modified from Shi and Blight[17]). The recording chamber consists of 5 wells. The end wells were filled with KCl (which simulates the intracellular condition), and the adjacent wells contained isotonic sucrose. The central well (which emulates the extracellular ionic space) was left dry. Rat sciatic nerve was placed over a piece of excised muscle (denoted *M*, central well) and set across all 5 wells. Isolating silicone grease and plastic slips were used to seal the well interfaces. Nerve action potentials were initiated by an electrode placed at predetermined distances (0, 2, 4, 6, and 8 mm) from the nerve centerline. The return stimulating electrode was placed in the KCl solution. Compound action potentials (CAP) were recorded with a pair of Ag/AgCl electrodes as illustrated. B, In vivo electrophysiology was conducted with a rat sciatic nerve model. The sciatic nerve was first exposed and a pair of Ag/AgCl hook electrodes was placed under the sciatic nerve proximal to the peroneal/tibial bifurcation. The current sink was placed on the retracted skin flap. Nerve stimulation was performed with an insulated electrode positioned 5 to 7 mm proximal to the recording electrodes. The stimulating electrode was placed on the musculature, on a plane perpendicular to the longitudinal nerve direction. This plane was either lateral (to the side) or above the nerve. The same 2-mm step increment was used for current-distance mapping. C, Diagram of anodic and cathodic connections. The activation function (shown right) is a mathematical prediction of action potential initiation and propagation. In cathodic stimulation, the area beneath the electrode is depolarized, but is flanked by zones of hyperpolarization. Conversely, the space beneath the electrode tip is hyperpolarized with anodic current. However, adjacent depolarized regions modulate action potential initiation. The size of the lobe potentials are current intensity dependent. Details of these results can be found in a previous paper.[14]

In Vivo Recording

Under anesthesia, rats were placed prone on an operating plate. An incision was made in the hamstring muscle and the sciatic nerve exposed (Fig. 1B). The adjoining nerve–muscle fascia was cut to isolate the sciatic nerve. However, the fascia was not excised to emulate its resistive influence. Retractors were used to maintain the surgical area. A pair of Ag/AgCl electrodes was used for stimulation and another pair of hook electrodes served for recording. The

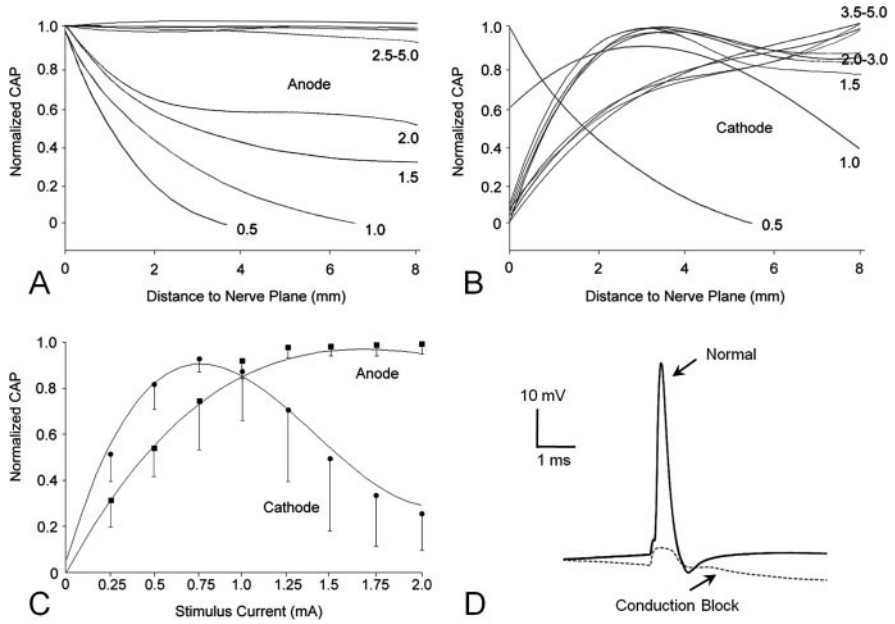

Figure 2. A, Ex vivo compound action potential (CAP) response to anodic stimulation. Each trace represents a best-fit function obtained from linear regression. Fixed-level current sweeps from 0.5 to 5.0 mA are shown. At each fixed current level, the CAP was normalized to the respective peak CAP. B, Current sweeps for ex vivo nerve and cathode stimulation. Noticeable conduction block occurred at close nerve-to-tip proximities. Full conduction block was observed at currents >2.0 mA. C, Ex vivo conduction response when electrode tip was in direct contact with the nerve (n = 5). In cathodic stimulation, an optimum stimulation window (between 0.5 to 1.0 mA) was observed. In contrast, anode connection conveyed a monotonic response, with the CAP increasing as a function of input stimulus. Beyond 1.25 mA, the CAP achieved maximum amplitude. Points on the curves represent mean ± SD. Note that for clarity, only the lower error bar is shown. D, Representative waveforms depicting a normal action potential (3.0 mA at a distance of 4 mm, black solid line) and an action potential during conduction block (3.0 mA at a distance of 0 mm, gray dashed line).

hook electrodes were slid underneath the sciatic nerve and raised slightly to separate the nerve from the surrounding muscle and connective tissue. The stimulation protocol was the same as the ex vivo setup, in which the electrode tip was advanced towards the nerve at 2-mm intervals (from 8 mm to 0 mm, in relation to nerve centerline). The return electrode was placed on the inner skin layer of the hamstring muscle. The experimental tissue was kept moist, but excessive fluid (blood, interstitial media) was wiped away with gauze. Minimum activation threshold was determined by visual confirmation of muscle twitch of the foot. At all stimulation intensities, care was taken to differentiate between local muscle contraction and actual nerve activation. The CAP was also monitored in this regard for verification. At the conclusion of the anode and cathode mapping experiments, the stimulating electrode was inserted into the sciatic nerve. The minimum current necessary for intraneural activation was tabulated.

Data Processing and Statistical Analysis

Cathodic and anodic stimulation maps were constructed with Mathematica (version 6, Wolfram) software. Mean CAP magnitudes (normalized) at each distance coordinate were plotted for every current sweep. A third-order best-fit function was used to interpolate values between sampled points. A color scheme was assigned on the basis of the relative CAP amplitudes. The maps were then merged with minimum threshold plots by using Adobe Photoshop CS3. Linear regression was used to create best-fit lines for the collected data. Regression analysis was made with MiniTab 15. Pairwise comparisons were done with a Student t test. A P value of <0.05 was considered to be statistically significant.

RESULTS

Ex Vivo Recordings

In anodic stimulation (n = 5), the CAP increased as the stimulating electrode was placed closer to the nerve. Maximum CAP amplitude was reached upon nerve contact. This was true at all stimulating intensities. Best-fit curves calculated from fixed-current sweeps are shown in Figure 2A. Note the gradual decrease in elicited CAP as a function of distance. At currents >2.5 mA, the electrophysiology was comparable for all input intensities.

In cathodic stimulation (n = 5), the CAP behavior was highly dependent upon electrode position and current magnitude (Fig. 2B). At a value of 0.5 mA, maximum CAP was found at close tip-to-nerve proximities. At 1 mA, nerve contact induced a partial conduction block at which the CAP decreased 60% in comparison with the same stimulus at 2 mm. At >1.0 mA, close tip-to-nerve proximities (<2 mm) produced an intensity-dependent block. At currents beyond 3.5 mA, the zone of optimum stimulation was several millimeters away from the nerve. Additionally, we performed a series of tests that investigated the optimum stimulation current during direct tip-to-nerve contact (Fig. 2C). The data describe a narrow window for optimum cathodic stimulation (0.5 to 1.0 mA). For the anodal arrangement, suprathreshold activation was achieved with currents beyond 1.25 mA.

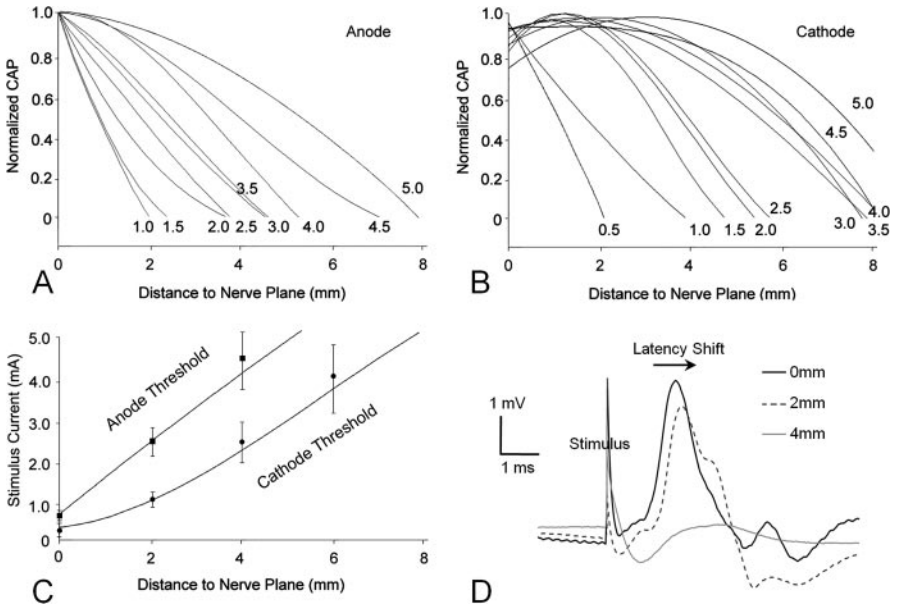

Figure 3. A, In vivo compound action potential (CAP) response to anodal stimulation. Each trace represents a best-fit function obtained from linear regression. Fixed-level current sweeps from 0.5 to 5.0 mA are shown. At each fixed current level, the CAP was normalized to the respective peak CAP. Note that at far tip-to-nerve distance, more current is required for activation. B, Cathodic stimulation plots for in vivo setting. Partial conduction block was observed when the electrode was in direct contact with the nerve. This is evident from the decrease in CAP magnitudes. C, Minimum current thresholds for both anodic and cathodic stimulation schemes (data truncated to 5.0 mA). Points on the curves represent mean ± SD. D, CAP waveforms depicting the latency shift as a function of stimulation distance. At closer stimulation distances, the latency times were shorter. Shown are CAP traces at 0, 2, and 4 mm distances for anodic stimulation (3.5 mA).

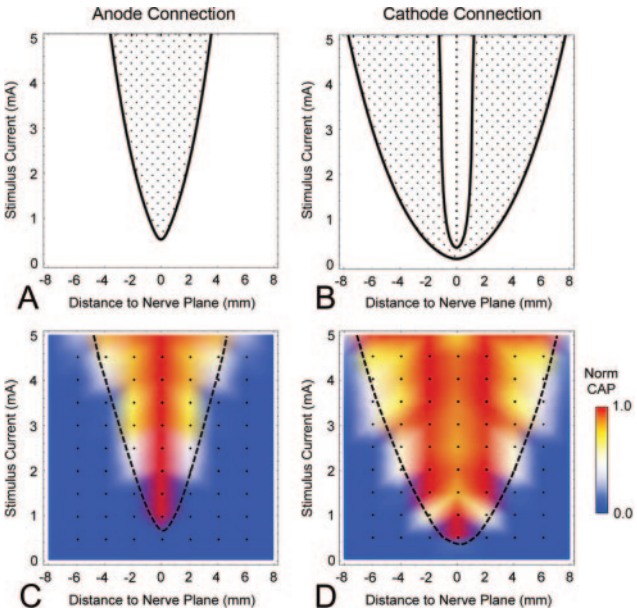

Figure 4. Theoretical activation maps as described by Johnson et al.[15] (reprinted with permission from *Anesthesiology*, Lippincott Williams & Wilkins) for A, anode and B, cathode connections. Shaded regions denote activation zones for different current–distance combinations. Note the area of conduction block (cathode connection) at close tip-to-nerve distances and higher currents. Experimental in vivo maps for C, anode and D, cathode configurations (n = 7). Relative compound action potential (CAP) intensities are shown with a colorimetric legend. At each fixed current level, the CAP was normalized to the respective peak CAP (Figs. 3A, 3B). The dashed lines denote the threshold for nerve activation (superimposed from Fig. 3C). Each dot on the graph also symbolizes sampled current–distance steps (0.5 mA or 2 mm, respectively). Areas between sampled points were interpolated with a third-order polynomial function.

Sample waveforms of normal and impaired action potentials are shown in Figure 2D.

We note that in the case of conduction block, the electrophysiology was highly erratic and variable. The shape of the action potential waveform was also affected.

In Vivo Recordings

Recordings taken from rat sciatic nerve mirrored the ex vivo data. In particular, anodic stimulation showed the same behavior for which maximum CAPs were elicited at 0 mm (nerve contact). Averaged best-fit traces are shown for current range of 0.5 to 5.0 mA (Fig. 3A). Cathodic stimulation also produced evidence of conduction block (Fig. 3B). At currents >1.0 mA, a decrease in the CAP was noted at 0 mm. The severity of block was on the order of 10%–20%, but increased with larger stimulus currents. Minimum activation threshold currents were also plotted against distance (Fig. 3C). The amount of current required for anodic stimulation was in general double the corresponding current with cathode connection. This ratio was relatively consistent for the specified distances. Latency, defined as the time from the stimulus to peak CAP, was shorter as the tip approached the nerve. The latency difference (Fig. 3D) was between 0.1 to 0.3 ms per 2 mm and was variable among animals. However, each animal showed a consistent decrease in latency (polarity independent) at closer nerve-to-tip measurements. In comparison with the ex vivo data, the normalized in vivo CAP degraded steeply as a function of distance for both anodal and cathodic stimulation. We ascribe this characteristic to geometric effects of the in vivo preparation (larger muscle volumes, current leakages, etc.).

In Vivo Current-Distance CAP Map

Individual current sweeps were replotted to form a 3-dimensional current–distance–CAP graph for both anode and cathode configurations (Fig. 4C, 4D, n = 7). The final 3- dimensional current–distance CAP graph yields quantitative measurement of the expected electrophysiology outcomes. The main departures between our values and previous simulations[15] lie primarily in the degree of conduction block.

Intraneural Versus Extraneural Thresholds

Results for extraneural or intraneural electrode placement were investigated in vivo. For anodic stimulation, the range of minimum activation currents was 0.45 to 0.90 mA with a mean of 0.63 ± 0.12 mA (n = 12) for extraneural cases. Intraneural thresholds were 0.20 to 0.44 mA, with a mean of 0.32 ± 0.09 mA (n = 8). With a cathode tip, the extraneural threshold values varied from 0.21 to 0.61 mA, with a mean of 0.34 ± 0.11 mA (n = 12). Intraneural stimulation decreased the activation values to 0.09 to 0.19 mA, with a mean of 0.12 ± 0.03 mA (n = 8). Regardless of polarity, there was a significant difference between the intraneural versus extraneural current thresholds ($P < 0.001$).

DISCUSSION

In clinical procedures such as nerve block, nerve stimulation is a common guidance technique used in localizing the nerve.[20] However, the accuracy and reliability of needle placement hinges primarily on precise current–distance relationships. The inconsistent results with nerve stimulation reported in the literature[11,22–25] imply anomalies between input current and the expected motor response. Indeed, factors such as electrode tip geometry, nerve-to-tip distance, amount of input current/duration, and connective tissue arrangement determine action potential initiation and propagation.[12,20] In this regard, computational models have been useful in elucidating the behavior of excitable membranes under various stimulation conditions. Two predicted outcomes of key clinical relevance are that (i) nerve activation with anodic stimulation requires significantly higher currents and (ii) strong cathodal currents near the axon (nerve) may lead to conduction block.[14–16]

In this work, we have used findings from previous computational simulations as the framework for experimental design. The reported CAP maps are consistent with simulated data.[15] As was expected, activation current increased at longer nerve-to-tip distances, and as highlighted in the graphical plots, anodic excitation required a doubling of stimulus intensity. This ratio echoes previous studies on polarity reversal.[22,26] Moreover, we also found corroborating evidence (ex vivo and in vivo) of a complex bioelectric response to cathodic stimulation. For instance, the CAP readings increased with gradual electrode advancement towards the nerve. But at closer nerve-to-tip distances, there was a decline in CAP amplitudes. This trend was valid for currents more than 1 mA. At less than 1 mA current, optimum electrophysiology was generally obtained with needle-to-nerve contact. Conversely, the current–distance relationship with anodic stimulation was monotonic. Greatest activation occurred when the electrode tip was in direct nerve contact. Progressively higher current was necessary to stimulate at farther distances.

The propagation block phenomenon with cathodic stimulation has been documented and hypothesized to be a spatial effect between current input and nerve geometry.[14] Injection of negative current (cathode) produces depolarization in the nerve region directly below the tip. However, this depolarized region is flanked by hyperpolarized membrane space[14,15] (Fig. 1C). If the stimulation is sufficiently strong, this hyperpolarization can prevent the action potential from propagating beyond the tip. This behavior has been addressed analytically and may be, in retrospect, suggested by others.[13] Indeed, failure to obtain motor responses in cases of confirmed needle to nerve placement can be explained by the block phenomenon shown in this study.

The primary difference between previous model data and our in vivo experimental results lies in the severity of conduction deficit at nerve contact. Complete action potential elimination was calculated in simulations by Johnson et al.[15] We observed full conduction block only in idealized situations (ex vivo). In addition, the often erratic (high variability) electrophysiology at small nerve-to-tip distances highlights the spatial sensitivity of the block phenomenon. We posit that in vivo current shunts from nearby connective tissue or interstitial fluid may alter current paths and support partial conduction. The larger conductive volume of the intact animal versus the ex vivo nerve–muscle preparation should also be noted. The profile for nerve activation decreased sharply with increasing distance with the in vivo model. The difference between the ex vivo and in vivo values can be explained by the constraints of the ex vivo geometry. For instance, the muscle preparation was small and the surrounding environment highly insulative. In contrast, the in vivo model more closely mimics the clinical setting, including endogenous current leaks, larger conductive volume, resistive elements such as connective tissue, etc. Conclusions regarding thresholds should thus be made accordingly. Nonetheless, our data are in good general agreement with previously studied axon models.

A significant concern with nerve stimulation is the potential for nerve penetration and subsequent intraneural anesthetic injection. Because nerve penetration should be avoided, we further investigated the difference in activation currents for extraneural and intraneural needle placement. We found the extraneural threshold to be 0.34 ± 0.11 mA for the cathode and 0.62 ± 0.12 mA for the anode (at 0 mm). These values are similar to other reports near 0.3 mA (cathode) and 1.0 mA (anode) for human femoral and interscalene blocks.[22] When migrating to intraneural stimulation, the threshold current decreased to 0.12 ± 0.03 mA and 0.32 ± 0.09 mA for the cathode and anode, respectively. Nerve penetration was also accompanied by a visual twitch of the innervated muscle. We believe the decrease in activation thresholds arises from the fascia and epineurial sheath. These components alter the local resistivity, and the sudden decrease in threshold current may signal a breach of the tissue barrier. This reduction in activation current was previously shown by Bigeleisen et al., who reported minimum activation values (cathode) of 0.6 mA extraneural cases, but only 0.3 mA for intraneural cases.[27] The collective animal and clinical data suggest that threshold/impedance monitoring could be used to avoid nerve puncture.

Finally, we report a small decrease in latency (anode/cathode) as the stimulating needle is moved towards the nerve. The absolute difference in latency for each distance increment (2 mm) was variable and on the order of tenths of milliseconds. Realistically, the variance in latency and the minute absolute difference may preclude its use as a quantitative tool, but qualitatively, latency differences do

reveal a forward or backward movement in relation to the nerve (but not absolute position).

This study and its findings have several important implications and limitations. Cathodic connection is the standard for nerve stimulation–assisted blocks due to low-threshold requirements. Cathodic currents between 0.2 to 0.5 mA have been generally used as a procedural end point.[21,28] However, cathodal conduction block when the needle and nerve are in close relation may be problematic. For example, a decrease or abolition of the CAP could indicate movement away from the nerve or actual nerve contact. In comparison, stimulation with the anode produces a CAP response that is inversely proportional to target distance. This desirable trait provides refined needle positioning, especially at near-nerve proximities. We caution that our initial results will require clinical evaluation.

Our approach was further constrained because of the use of an open-dissection model versus a closed-tissue model. We measured the nerve action potential rather than the more clinically relevant compound muscle action potential. Lastly, the stimulation electrodes used may be slightly different from commercial needles. These experimental variables were chosen to better match the idealizations and outcomes generated by computational simulations. Therefore, the applicability of the full findings to human patients remains unknown.

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