Controlled Nerve Ablation With Direct Current: Parameters and Mechanisms

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***Abstract*—Spastic hypertonus (muscle over-activity) often develops after spinal cord injury or stroke. Chemodenervating agents such as Botulinum toxin A (BtA) and phenol are often used to treat this condition. We have previously shown that the use of direct current (DC) to create controlled lesions of peripheral nerves may provide a means of reducing spastic hypertonus. Here, we explored a range of stimulation parameters that could be used clinically. Nerves were lesioned with DC in chronically implanted animals and the outcome was tracked over many months. In addition, we used DC to ablate nerves in animals with decerebrate rigidity (an animal model of spastic hypertonus) and we explored the possible mechanisms of DC nerve ablation. We found that nerve ablation with DC was effective in reducing hypertonus. Some stimulation paradigms were more likely to be clinically acceptable than others. Furthermore we showed that nerve regeneration occurs in the months following DC nerve ablation and we demonstrated that the ablation procedure is repeatable, much like BtA treatment. Regarding mechanism, our results did not support the hypothesis that DC caused nerve damage by overactivating sodium channels. Rather, the mechanism of damage seems to be related to changes in pH.**

***Index Terms*—Direct current (DC), nerve lesion, spastic hypertonus, stroke.**

I. Introduction

ONE of the most debilitating outcomes of stroke and spinal cord injury (SCI) is the loss of motor function. This may be exacerbated by spasticity, a chronic over-activity of muscles. Spasticity is associated with reduced range of motion (ROM), pain, and contractures [1], [2]. Several studies have shown that spasticity can impede activities of daily life (ADL) [3]–[5].

Spasticity develops in approximately 20%–30% of stroke survivors 6–18 months post-stroke [3], [4], [6], [7]. Stroke prevalence in the United States (U.S.) alone is estimated at 7 million individuals [8]. Of the estimated 270 000 individuals living with SCI [9], over 60% develop spasticity following injury, of whom more than half are medically treated. The incidence of spasticity is greater in those with cervical or high thoracic SCI [10]. With a decreasing incidence of mortality resulting from a stroke event [8] and the high prevalence of individuals with SCI requiring care, the burden on the health care system is increasing.

Current treatments for spasticity include physical and occupational therapy, anti-spastic medications, and chemodenervation [11]. Physiotherapeutic methods such as stretching, range of motion (ROM) exercises, and casting require a considerable time commitment, and are of limited efficacy and duration [12]. Whole body vibration has not lived up to its initial promise [13], [14] though a new study indicates that focal muscle vibration may be beneficial [15]. Common oral anti-spastic drugs such as Dantrolene, Tizianidine, and Baclofen can cause adverse side effects such as muscle weakness, hepatotoxicity, dizziness, and sedation [16]–[18] and they do not reduce spasticity in all patients [10], [19]. A recent review concluded that while Baclofen and Dantrolene reduced muscle tone, there was no evidence that this had a functional impact [20]. Baclofen can be delivered intrathecally via a surgically-placed pump, allowing a lower dosage than oral medication, which reduces systemic side-effects, however, other complications such as infections around the implants may occur [21].

Chemodenervation agents such as phenol and Botulimum toxin type A (BtA) are used to block nerve conduction. Phenol injections have a rapid onset but often have painful side effects [22], [23]. BtA treatment is costly, may take up to two weeks to take effect and usually lasts only a few months [24], necessitating repeated, costly administrations [25]. BtA has proven effective in managing spasticity, but this does not necessarily improve motor function [26]–[28]. Furthermore, continuous use of BtA results in muscle atrophy and loss of muscle tissue in both the target muscle and muscles elsewhere in the body [29].

Direct current (DC) has been used experimentally to block conduction in peripheral nerves, but it was deemed unsuitable for clinical use on the assumption that complete recovery was essential [30]. However, just as long-term nerve ablation with Phenol is useful clinically, so could DC ablation, with the advantage that the amount of ablation could be controlled. In a previous publication [31] initial results of complete and partial nerve ablation were presented. In the present study we explored a range of stimulation parameters with the goal of identifying combinations of current and duration that would be effective and clinically acceptable. DC nerve ablation was performed in acute experiments in anesthetized, decerebrate, and chronically implanted animals. Two possible mechanisms of DC ablation were explored.

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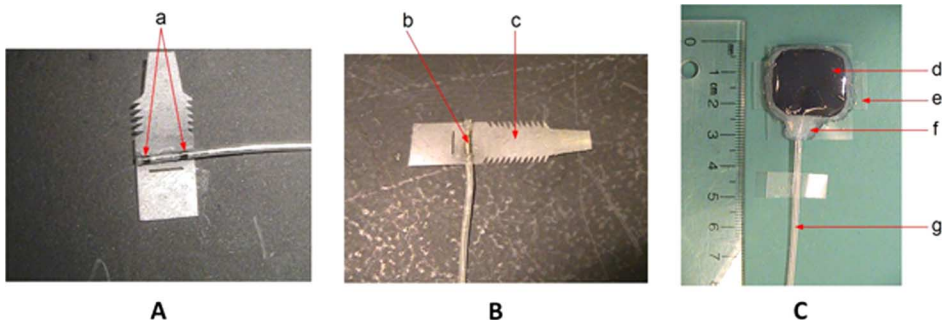

Fig. 1. Nerve cuff electrodes. A) Proximal cuff used to elicit test muscle twitches; *a)* Bipolar terminals formed by tight coils of stainless steel wire emerging from the silicone tubing of the lead (cuff, in the form of a tie-wrap, is shown open). B) Monopolar Pt-Ir nerve cuff, used to deliver DC for nerve ablation; *b)* Terminal formed by a tight coil of Pt-Ir wire soldered to the stainless steel wire emerging from the silicone tubing of the lead; *c)* Silicone nerve cuff. C) Subcutaneous port and lead; *d)* Black conductive layer under silicone sealant layers; *e)* Silastic backing sheet; *f)* Silicone sealant; *g)* Coiled Pt-Ir wire inside silicone tube filled with sealant.

II. Methods

All procedures were approved by the University of Alberta Animal Care and Use Committee.

A. Nonrecovery Experiments in Rabbits

Seven white New Zealand rabbits were used in single, nonrecovery experiments. Surgical-plane anesthesia was induced with gaseous Isoflurane delivered through a mask. A tracheotomy was performed, allowing anesthesia to be maintained via an endotracheal tube. The left sciatic nerve was exposed through an incision overlying the hamstrings muscle. The common peroneal nerve (CPN) was separated from the tibial nerve and transected. Two nerve cuff electrodes were attached to the tibial nerve branch: a proximal cuff to deliver test stimuli and a distal cuff to deliver DC. The cuffs each comprised a strip of silicone in the form of a "tie-wrap" (Fig. 1). The leads were made of insulated, multi-stranded stainless steel wire (AS632, Cooner Wire, Chatsworth, CA, USA) coiled inside a silicone tube, filled with silicone sealant (RTV 118, Momentive Performance Materials, Waterford, NY, USA) [31]. The proximal cuff contained a pair of terminals formed from the stainless steel lead wires [Fig. 1(a)]. The distal cuff, which was used to deliver DC, contained a Platinum Iridium (Pt-Ir) terminal [Fig. 1(b)].

At the input end of the leads, two types of connector were used, 1) conventional 2-mm connectors external to the body; 2) subcutaneous ports aimed at clinical applications, where repeated sessions of nerve ablation are anticipated [Fig. 1(c)]. Hypodermic needles, insulated except for their tips, were inserted into the ports through the skin, providing temporary electrical connections to the nerve ablation lead.

The port comprised two 2×2 cm stainless steel plates (SS316 flat pack, 0.01 in, Mauldin products, Kemah, TX, USA). An electrode lead was soldered to one of the plates and the plates were glued together with silver conductive epoxy (8331-14G, MG Chemicals, Surrey, BC, Canada), sandwiching the solder joint between them. A 2×2 cm sheet of conductive rubber (C5020PF CMP Ltd, Scarborough, Toronto, ON, Canada) was stuck to one of the plates with the same epoxy. A nonconductive silicone sheet (0.010 in SSF-METN-750, Speciality Silicone Fabricators, Paso Robles, CA, USA) was stuck to the other plate with silicone sealant. Finally, the port and emerging section of lead were coated with silicone sealant.

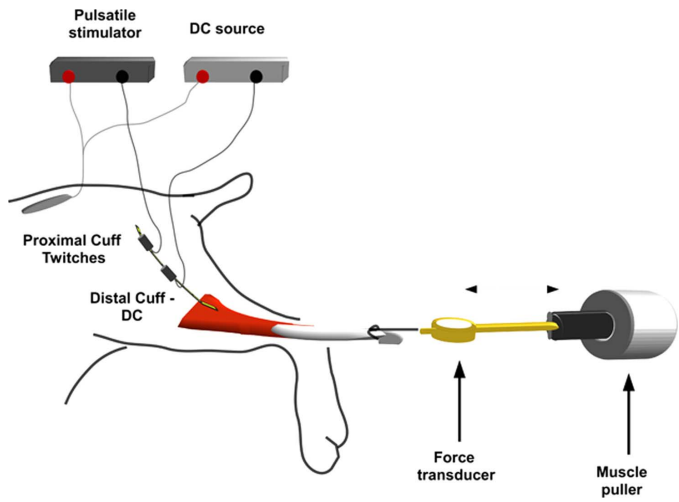

Fig. 2. Nonrecovery experiments in anesthetized rabbits and decerebrate cats. Leg was stabilized in a frame. Triceps surae tendon was connected to a muscle puller via a force transducer. Nerve cuffs were attached to the tibial nerve. Muscle was stretched cyclically while test muscle twitches were elicited by pulses delivered through the proximal cuff. DC was delivered through the distal cuff to ablate the nerve in a controlled way.

The rabbit was suspended prone in a stereotaxic frame, its left knee stabilized with a clamp. The triceps surae tendon was exposed through a skin incision, detached with a portion of the calcaneal tuberosity and secured to a force transducer with silk suture. The force transducer and a displacement transducer were part of an electromagnetic, servo-controlled muscle puller that stretched the muscle cyclically through its physiological range (Fig. 2). This allowed the muscle's maximal twitch force to be captured in each cycle. Charge-balanced current pulses (200 μs, 2/s) were applied through the proximal cuff to elicit test muscle twitches.

Current, force and displacement signals, along with current and voltage signals from a feedback-controlled DC generator were sampled at 500 samples/s with a digital oscilloscope (TDS3014B, Tektronix Inc., Beaverton, OR, USA). Segments of data 20 s long were sampled at intervals of 1–5 min. DC was

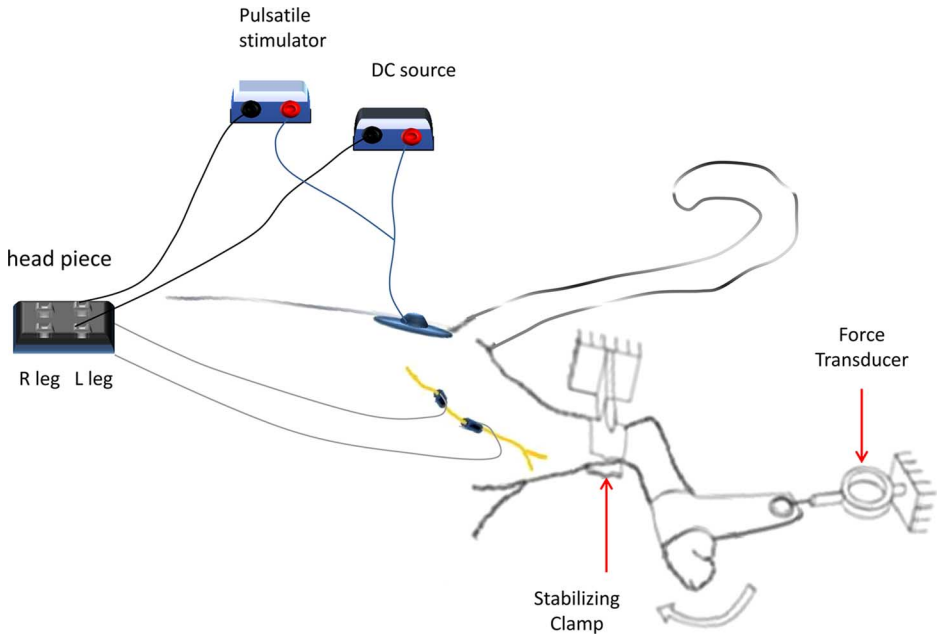

Fig. 3. Partial DC ablation of CPN in anesthetized cat. Hind limb was held by a clamp, foot was connected to a force transducer. Test pulses (200 μs, 2 Hz) and DC were delivered through proximal and distal nerve cuffs respectively. Twitch force was measured before, during and after DC delivery.

delivered from time to time through the distal cuff at amplitudes ranging from 0.5 to 2.5 mA. The digitized signals were downloaded to a desktop computer via a local area network.

B. Nonrecovery Experiments in Decerebrate Cats to Test DC Abolition of Rigidity

In two cats, the surgery described in Section II-A was performed. A jugular catheter was implanted to allow drug administration. The cat was placed in a frame as in Fig. 2. The skull was trefined and an intercollicular decerebration was performed, after which anaesthesia was discontinued. A pair of electromyogram (EMG) wire electrodes was implanted in the triceps surae muscles and connected to an amplifier (Iso-DAM8A, WPI, Sarasota, FL, USA: gain 1000, bandpass 10 Hz–3 Khz). The EMG signal was further amplified, filtered (high pass 10 Hz), full-wave rectified and filtered (low-pass, 3 Hz). The length, force and EMG signals were sampled at 5000/s in 2 s segments. When rigidity had developed, baseline responses to stretch were recorded and DC was applied (3 mA for 1.5 min) to ablate the nerve. Data were obtained for 40 min following DC ablation.

C. Procedures in Chronically Implanted Cats Under Brief Periods of Anesthesia

The implant procedure [31] is briefly reviewed here. In two cats, pairs of nerve cuff electrodes [Fig. 1(b)] were implanted on the CPN of each leg under isoflurane anesthesia. In the first cat, the terminal in the distal cuff was Pt-Ir wire soldered to the stainless steel wire that formed the insulated lead. The solder joint failed a few months after implantation, so in the second cat, a single continuous Pt-Ir wire formed both the lead and the terminal. The leads were passed subcutaneously to a connector embedded in a percutaneous headpiece attached to the skull. At extubation, the analgesic ketoprofen (0.5–1 mg/kg SC) and the antibiotic Convenia were administered. The cats were kept warm in a heated enclosure. The analgesic Hydromorphone (0.05–0.1 mg/Kg SC) was administered 6 h later.

After implantation, two procedures were performed during brief periods of isoflurane anesthesia.

1) *Force monitoring:* Test twitches of the pretibial muscles were monitored weekly before and after DC nerve ablation. The anesthetized cat lay prone on a heavy metal base, its hindlimb held in a padded clamp attached to the base (Fig. 3). A 1 cm wide strap was looped around the metatarsals and attached to a force transducer oriented at right angles to the foot. Biphasic, charge-balanced, constant-current pulses (200 μs, 2/s, 2T) were delivered through the proximal nerve cuff. A self-adhesive gel electrode (Kendall ES40076) on the back served as the indifferent. An angle-force curve was constructed by measuring twitch forces at several ankle angles. The force transducer was then magnetically clamped to the base at the optimal angle. Force, current and voltage signals were sampled and stored as in Section II-A.
2) *DC nerve ablation:* This was done on one occasion in one cat and on two occasions in the other cat. A custom stimulator delivered DC via the distal cuff. Force monitoring (Procedure 1) was performed before, during and after DC delivery. A moist pad surface electrode (3 cm diameter) applied to the shaved skin on the back served as the common indifferent in this case.

D. Nonrecovery Experiments in Rabbits and a Cat With Lidocaine Blockade of CPN to Elucidate Mechanism of DC Ablation

The purpose of these experiments was to test the hypothesis that DC ablation is due to overactivation of sodium channels and that therefore Lidocaine blockade of these channels should protect nerves from DC-induced damage.

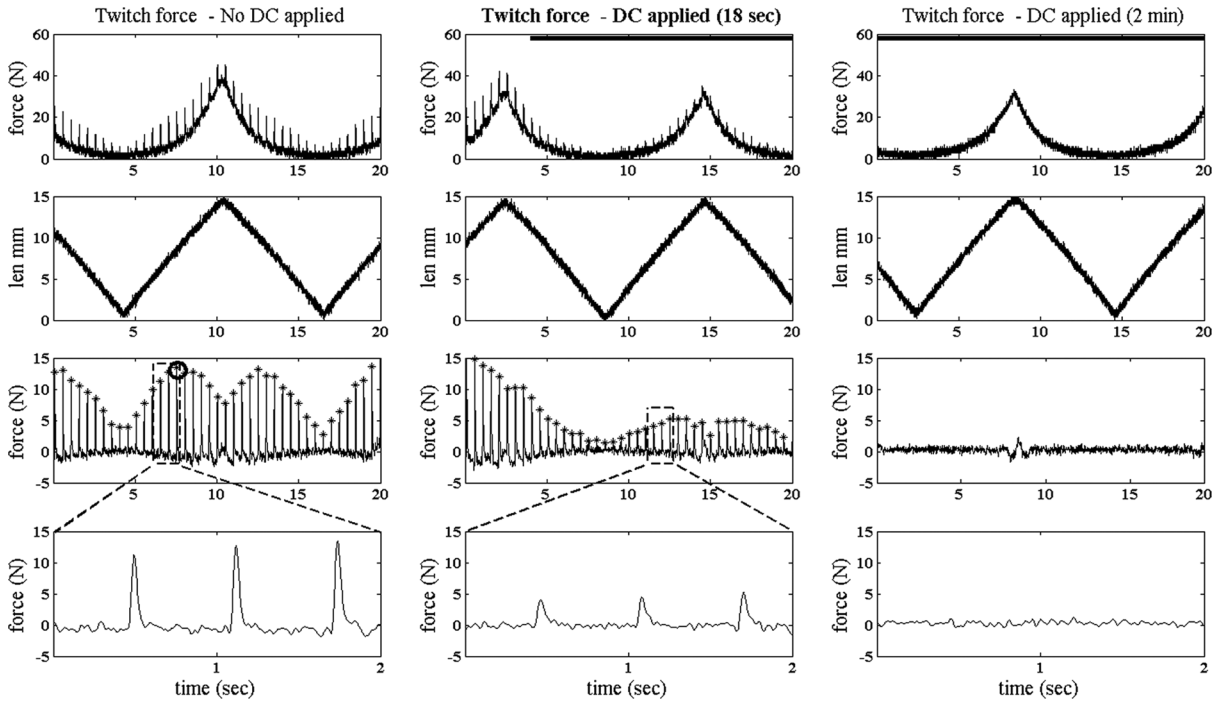

Fig. 4. Muscle force and displacement, before, during and after DC ablation. Top row: Force responses. Black bars show period of DC application. Second row: Imposed displacement. Third row: Twitch forces after the passive force was removed by filtering. The peak force in each twitch (asterisks) and the maximal peak twitch force within each stretch cycle (circled asterisk) was automatically identified by a software program.

Two rabbits and one cat were anesthetized and two nerve cuff electrodes were placed on each CPN as in Section II-A. Test muscle twitches were elicited and signals were sampled and displayed as in Section II-A. The optimal ankle angle was determined as in Section II-C. Twitch responses were recorded for several minutes until their amplitudes settled to a stable baseline. An initial dose of 0.2 ml of 1% Lidocaine solution (Xylocaine, AstraZeneca) was injected into the distal cuff with a 28G hypodermic needle over a period of 2–3 min. This initial dose was applied in order to establish the time T_1 from complete nerve block to recovery. As soon as the Lidocaine had abolished muscle twitches, the nerve was flushed with 10 ml of isotonic saline in and around the cuff. When muscle twitches had recovered to 60%–80% of baseline values, a second identical dose of Lidocaine was injected into the distal nerve cuff. When muscle twitches were abolished, the nerve was again flushed with 10 ml isotonic saline and DC was applied (3 mA for 4 min). The responses to test stimuli applied through the proximal cuff were then monitored for at least $2 * T_1$.

E. Data Analysis

1) *Nonrecovery experiments in rabbits.*
Data analysis methods were described previously [31], so only a summary is provided here. Force, displacement, current, and voltage signals were sampled and stored as described in Section II-A. A custom MATLAB program was used to detect the maximal twitch force within each muscle stretching cycle (Fig. 4). Segments of data (20 s) were sampled every 0.5–10 min and the maximal twitch force in each cycle was computed and displayed.

2) *Chronically implanted cats and Lidocaine experiments in rabbits.*
Data segments, each 20 s in length, were collected as in Section II-A and the mean twitch force amplitude was computed and normalized to the mean twitch amplitude in sessions prior to the first DC ablation.

3) *Charge density calculations.*
In previous studies examining safe stimulation of nerves, the charge density per phase was found to be the most relevant variable [32]. To calculate charge density, we estimated the surface area of the wire in DC nerve cuff terminals that was actually in contact with the nerves, assuming that half of each coil of the wire forming the terminal was in contact with the nerve. The terminal of the cuff used in the first acute rabbit experiment had an estimated surface contact area of $0.3 * 0.5 * \pi/2 = 0.236$ cm^2. That of the cuffs used in the rest of the experiments had estimated surface areas of 0.093 cm^2.

III. Results

A. Exploration of DC Parameters

In previous published experiments on DC nerve ablation [31], the DC amplitudes tested were nearly all in the range 0.1–0.5 mA. In the present experiments, we explored the possibility of applying higher levels of DC (up to 2.5 mA) for shorter durations. Seven rabbits were tested with the currents and durations in Table I.

TABLE I
DC AMPLITUDES AND DURATIONS EXPLORED IN SEVEN ACUTE RABBIT EXPERIMENTS

Rabbit	#repetitions * duration(sec) * current(mA)	total charge C	surface area cm^2	total charge density C/cm^2	total time sec	mean current mA	Final force attenuation %
1	6*120*0.75	0.54	0.236	2.3	720	0.75	100
2	14*120*0.75	1.26	0.093	13.5	1440	0.88	63
3	1*20*2 + 5*30*2 + 3*40*2 + 1*30*2.5 + 2*60*2	0.90	0.093	9.6	440	2.03	100
4	3*30*1 + 3*30*1.5 + 3*30*2 + 3*30*2.5	0.63	0.093	6.8	360	1.75	90
5	3*45*1 + 3*60*1 + 3*60*1 + 3*90*1 + 2*120*1	1.25	0.093	13.4	1005	1.24	100
6	4*30*2 + 4*60*2 + 3*90*2	1.26	0.093	13.5	630	2.00	80
7	1*30*1.5 + 7*60*1.5	0.68	0.093	7.3	450	1.50	60

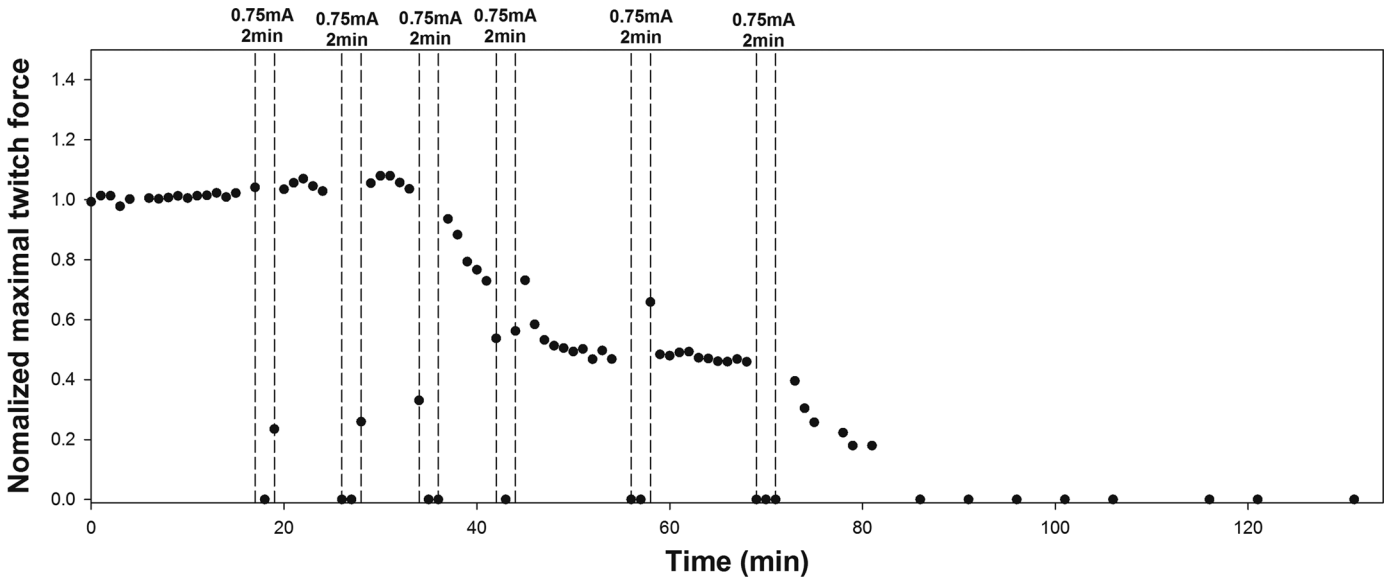

Fig. 5. Rabbit 1. Changes in twitch force during and after six episodes of DC (horizontal bars at top) applied at an amplitude of 0.75 mA for periods of 120 s. Twitch force was abolished during each DC application, but recovered quickly when DC ceased.

The time course of ablation with identical DC parameters varied between animals. In rabbits 1 and 2, 0.75 mA DC was repeatedly delivered to the nerve for durations of 120 s. In rabbit 1 (Fig. 5), twitches were abolished while DC was applied, but they recovered quickly each time DC ceased. Attenuation of twitch force was graded, with a reduction to 50% of baseline after four applications and complete abolition shortly after the sixth application. In rabbit 2 (Fig. 6), the very first application of DC reduced twitch force to $\sim 50\%$ of baseline, yet numerous additional applications did not increase the attenuation. We wondered whether the variability in the effect of identical levels and durations of repeated DC applications either within one session or between sessions in different animals might have been due to variations in the contact area of the electrode terminal with the nerve. For example small hydrogen gas bubbles forming during DC could reduce the interface area, raising the electrode impedance. To address this question we computed the electrode impedances from the voltage and current signals in the trials of Figs. 5 and 6. In the trial of Fig. 5, the impedance was 5.72 kΩ with a standard deviation of 0.46. In the trial of Fig. 6, the impedance was 3.65 kΩ with a standard deviation of 0.21. The corresponding coefficients of variation (8% and 6%, respectively) are modest and do not support the idea of significant changes in impedance in successive applications of DC. The inability to completely abolish twitches in this rabbit led to a strategy in subsequent experiments where either the amplitude or duration of DC was increased if no force reduction was observed after two or three applications.

1) *Constant DC amplitude and variable duration.*
In rabbits 3, 5, 6, and 7, DC durations were increased in successive trials while the amplitude remained constant (1 and 2 mA). In two of these experiments, one of which is shown in Fig. 7 (rabbit 3), after an initial large reduction in twitch force, smaller reductions occurred in subsequent DC applications. Recovery times gradually increased and after the final DC application no recovery occurred.
2) *Constant DC duration and increasing amplitude.*
In rabbit 4, the duration of DC application remained constant and the amplitude was progressively increased. A gradual controlled reduction of the maximal twitch force was observed (Fig. 8).

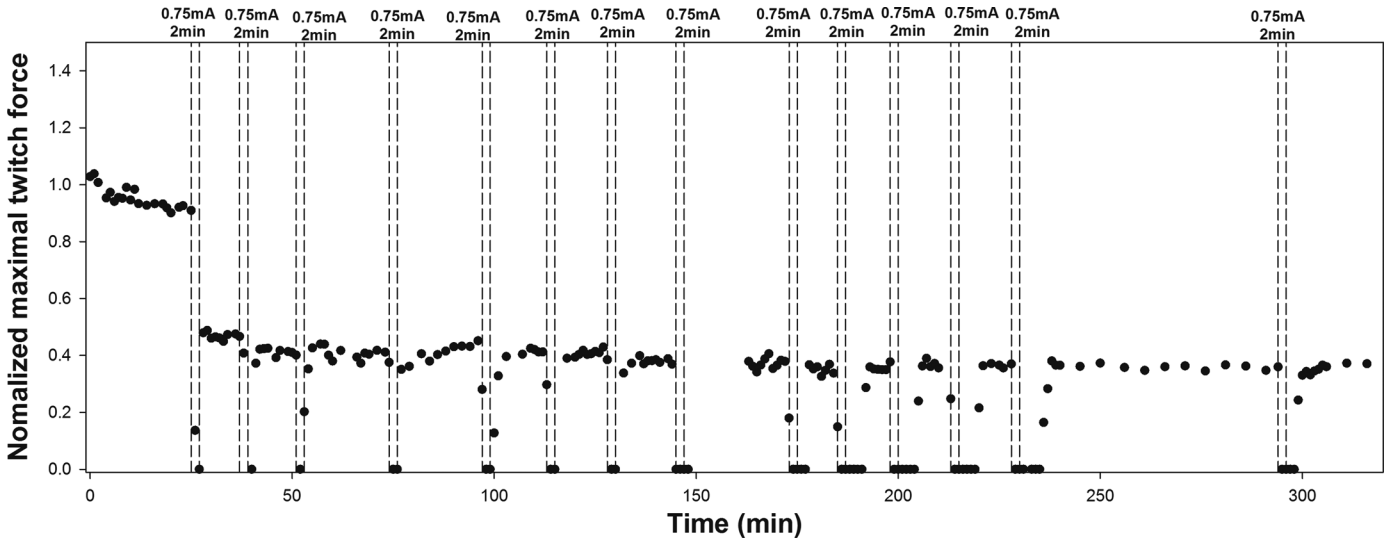

Fig. 6. Changes in twitch force during and after 14 episodes of DC, 0.75 mA for 120 s, as in Fig. 5. Reduction of the maximal twitch force to 50% of baseline value was evident immediately after the first DC application. No further substantial reduction occurred with 13 additional DC applications. As in Fig. 5, during each DC application, nerve conduction was completely blocked. Recovery of force after consecutive DC applications became prolonged.

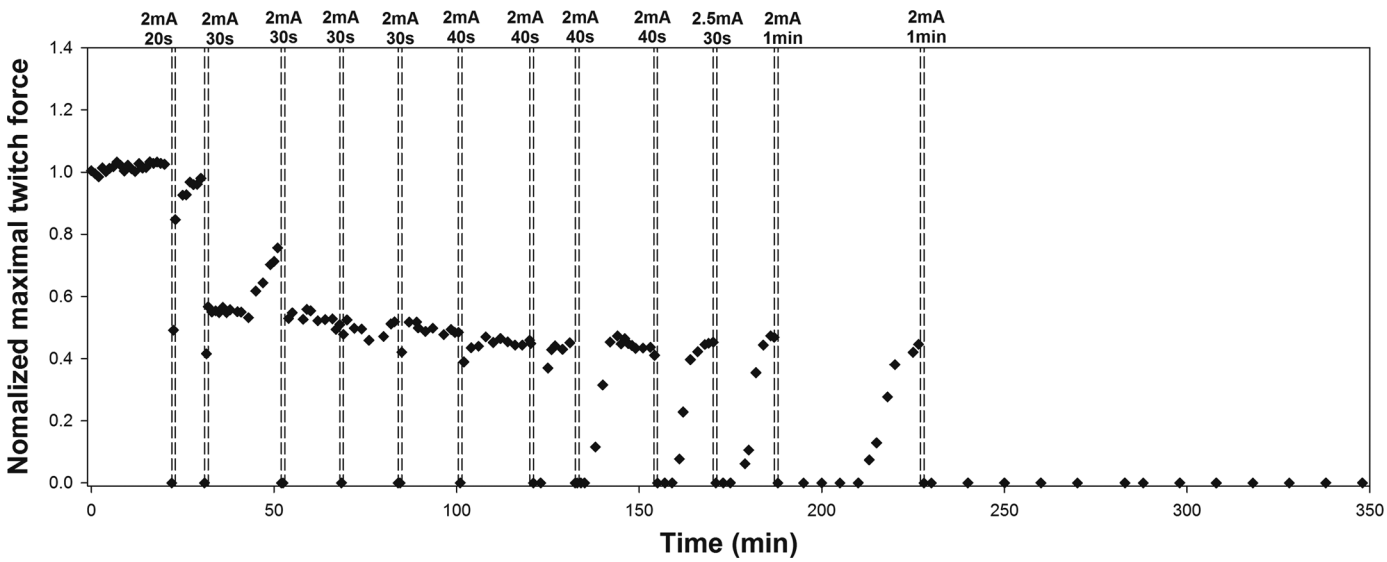

Fig. 7. Changes in twitch force during and after DC applications of increasing duration. In all but one case, the DC amplitude was 2 mA. Twitch force dropped to 55% of baseline after the second DC application. After the final DC application, force was completely abolished and did not recover for the remaining 120 min.

3) *Testing the subcutaneous port.*
In the experiments described above, the lead wires emerged through the skin. In a clinical application, an implanted subcutaneous port connector would enable minimally-invasive repeated DC ablations. In four rabbits we tested subcutaneous ports such as the one shown in Fig. 1. Fig. 9 shows the results of one such trial in which 1.5 mA of DC was applied percutaneously via an implanted port. A gradual reduction in force was observed with successive DC applications.
4) *Charge and charge density.*
In previous experiments in which alternating currents (AC) were applied to brain tissue via microelectrodes, the charge per phase and the charge density per phase were found to interact to produce nerve damage. [32]. Damage occurred when the product of μC per phase and $\mu\mathrm{C}/\mathrm{cm}^2$ per phase exceeded 80. Below this value, current could be applied for many hours without causing damage, even though the total charge and charge densities then became very high. It is not possible to compare these results directly to our DC ablation trials, where there was no equivalent of "phase." However, we analyzed the results in Table I to see if there were any obvious relationships between charge, charge density and the final attenuation of test muscle twitches after repeated DC ablations. No clear correlations emerged in scatter plots of the different combinations (not shown here). For example, in rabbits 1 and 2 (Figs. 5 and 6) the charge density per DC application in rabbit 1 was lower than that in rabbit 2, as was the total charge density, yet complete ablation was reached after six applications in rabbit 1 whereas in rabbit 2, even after 14 DC applications at the higher charge density, nerve ablation was still incomplete.

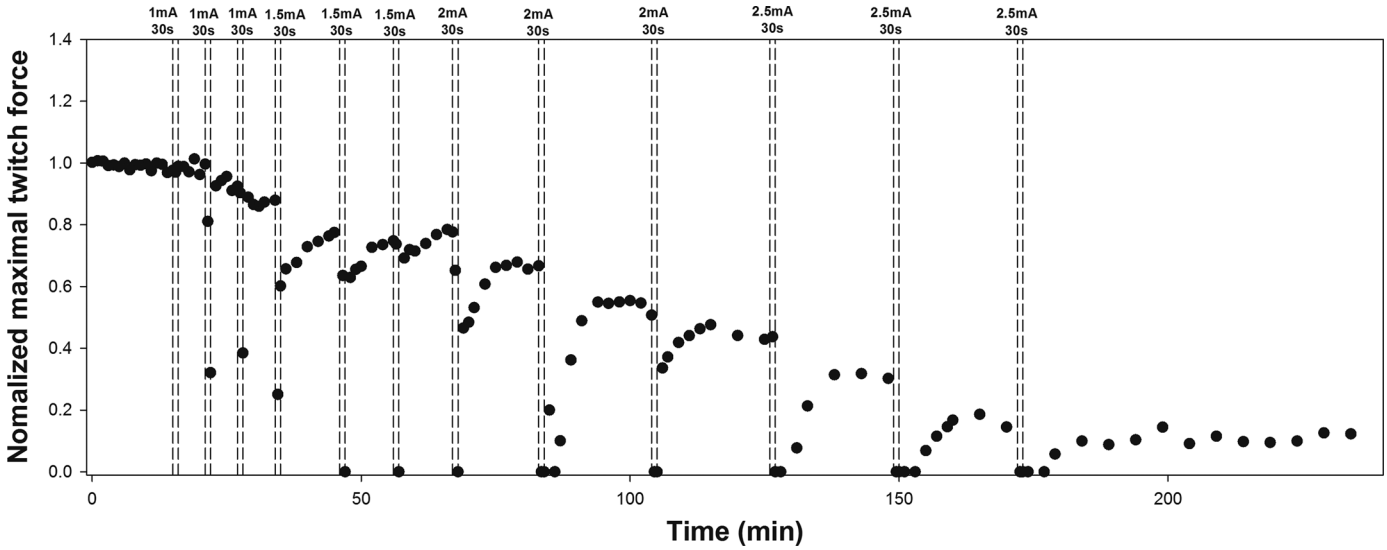

Fig. 8. Changes in twitch force during and after episodes of DC at progressively increasing amplitude. In this experiment, 1 mA of DC was initially applied for 30 s. Graded reduction in twitch force was observed as the DC amplitude was increased. Twitch force was eventually reduced to $\sim 10\%$ of baseline values after 12 applications.

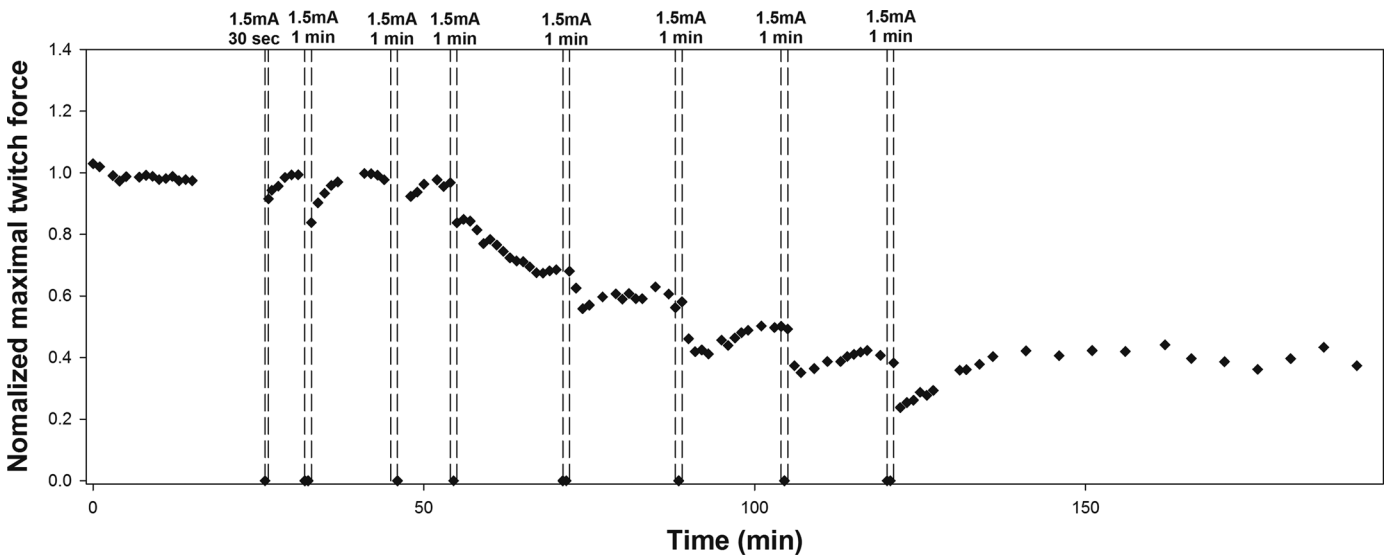

Fig. 9. Changes in twitch force during episodes of DC delivered through a subcutaneous port connector. Initially, 1.5 mA of DC was applied for 30 s. Consecutive applications lasted 60 s. Progressive attenuation was similar to that in Figs. 8 and 9, but in this case, a gradual reduction was evident without increases in DC duration or amplitude. After eight DC applications, the force was reduced to $\sim 40\%$ of baseline value.

B. Decerebrate Preparation

In one cat, decerebrate rigidity appeared about an hour after the procedures described in Section II-B. Rigidity remained stable, as judged by reflex EMG responses to muscle stretch prior to DC application, and after this, the responses of the contralateral leg to sensory stimulation of the foot. Baseline values of force and EMG were recorded for 4 min. DC was then applied for 1.5 min and recording continued for another 40 min. Fig. 10 shows the rectified EMG responses to muscle displacement prior to DC onset (A), at the onset of DC (B) and 40 min after DC was turned off (C). At the onset of DC [Fig. 10(b)], EMG activity additional to the stretch-evoked responses occurred, indicating that DC was eliciting sensory input. This was also seen in the cat that did not develop rigidity. These additional responses quickly subsided and by 1 min after DC onset, even the stretch-evoked responses were abolished and remained so for the subsequent 40 min of observation.

Fig. 11 shows the rectified EMG and force responses to muscle displacement before DC (A) and 40 min after DC (B). Only the passive component of force in response to muscle stretch remained in Fig. 11(b).

Fig. 12 shows the time course of mean rectified EMG and peak active muscle force in each stretch cycle before, during and after DC was applied to the nerve. The active force was calculated by subtracting the average time course of three cycles of passive force (Fig. 11(b), blue signal). The peak active forces in each cycle throughout the experiment were then plotted in Fig. 12. The mean EMG in each cycle was calculated from the area under the rectified EMG signal. EMG and force were greatly attenuated during DC application but not entirely abolished, as they had been in some of the DC applications in the anesthetized rabbits.

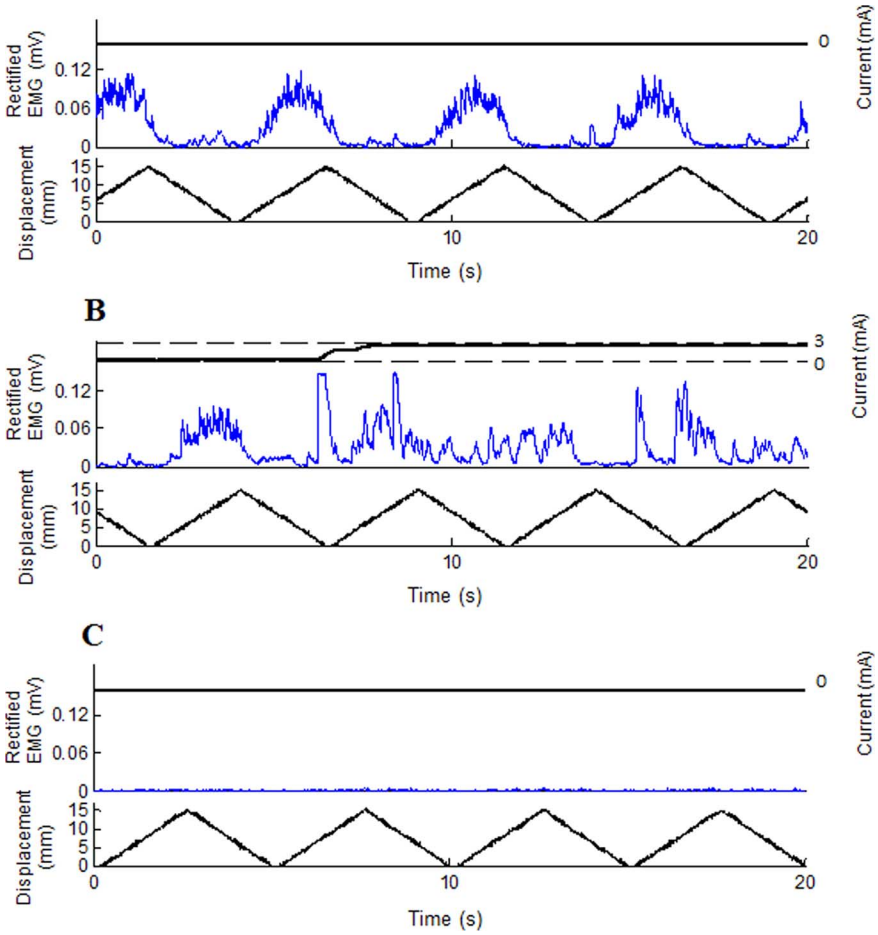

Fig. 10. EMG responses to muscle displacement (positive incline indicates stretch) in the decerebrate cat that developed rigidity. 3 mA DC was applied for 1.5 min. A: Before DC onset the EMG response was correlated with displacement. B: At DC onset (3 mA) the EMG activity became uncorrelated, indicating an additional component of EMG elicited by the DC. C: EMG response to stretch 40 min after cessation of DC at which time, EMG activity was virtually absent.

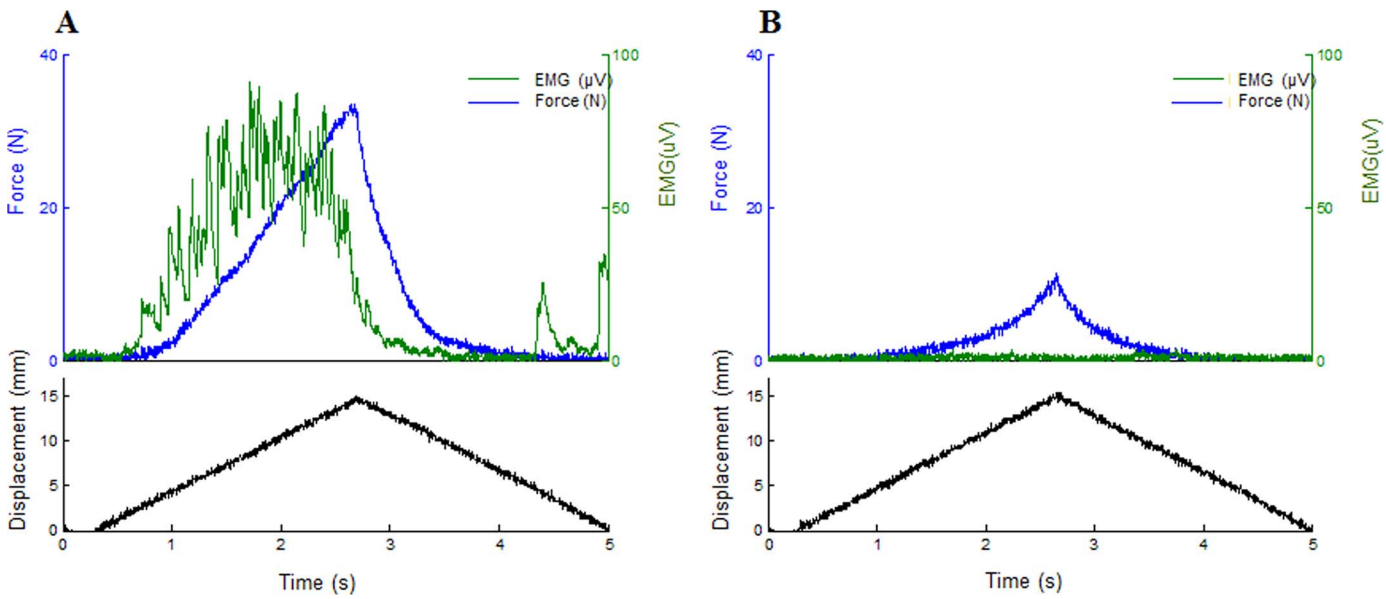

Fig. 11. EMG (green) and force (blue) responses to muscle displacement (black, stretch upward) in single stretch cycles (A) before and (B) 40 min after DC application (3 mA for 1.5 min). EMG responses in (B) were absent and only the passive force resulting from the stretch of the inactive muscle was observed.

C. DC Delivery via Implanted Ports and Nerve Cuffs

In the first cat, 17 weeks post-implantation, baseline force measurement and DC ablation were performed in a single session. After baseline force had been monitored, 0.5 mA DC was delivered for 10 min. Force continued to be monitored for 30 min, after which anasthesia was discontinued. In five subse-

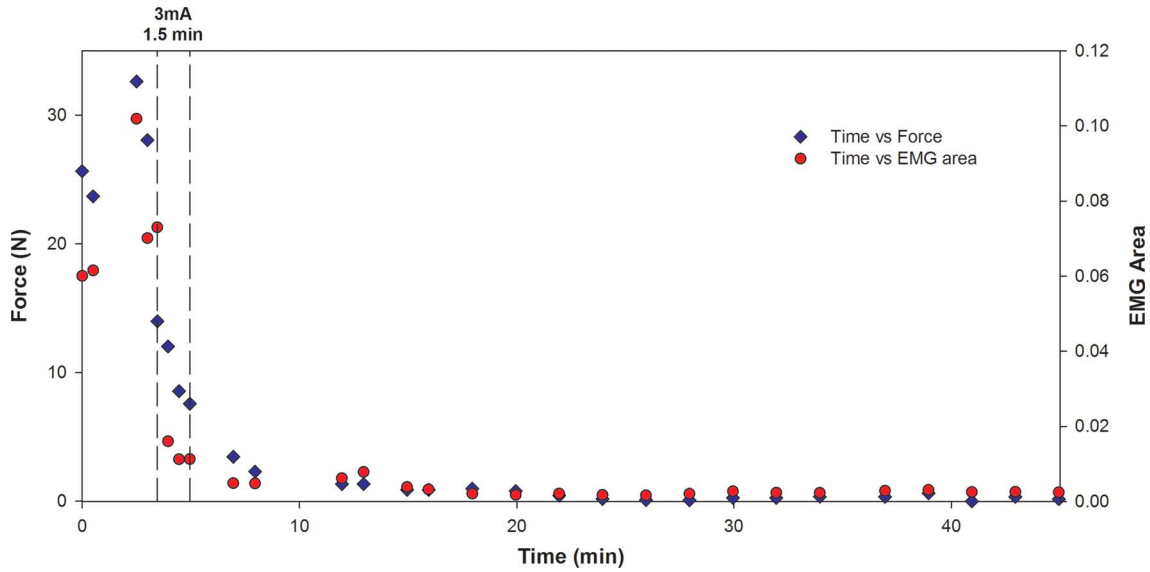

Fig. 12. Time course of mean rectified EMG (red) and peak active force (blue) per stretch cycle in a decerebrate cat. Two dashed vertical lines indicate DC application (3 mA for 1.5 min). Both the EMG and active force responses to stretch diminished to zero over a period of 15 min after DC was applied to the nerve, and remained absent for the following 25 min of observation, indicating that DC had abolished decerebrate rigidity in this muscle.

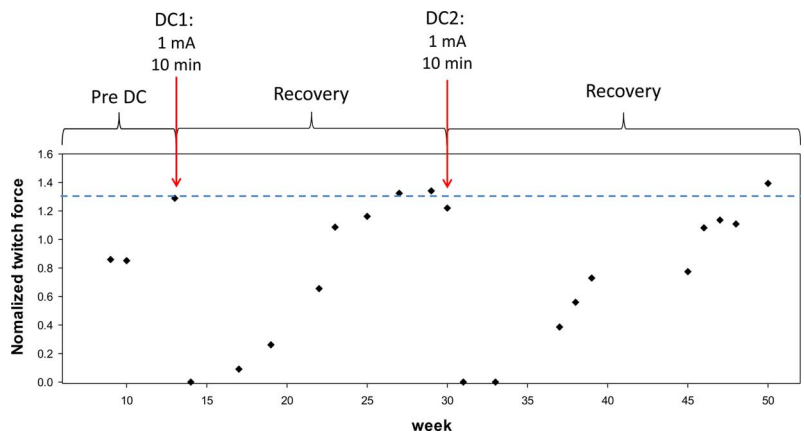

Fig. 13. Mean twitch forces in a chronically implanted cat in the weeks before and after two sessions in which DC was delivered to the CPN. Each dot represents the mean twitch force derived from five data segments recorded in a single force measurement experiment as described in 2.6.2. First delivery of DC (DC1) abolished twitch force and this was maintained in the following week. Force gradually recovered over the subsequent 13 weeks. Second application of DC (DC2) resulted in a similar time course of twitch decline followed by recovery.

quent weekly sessions, the mean twitch force was fairly constant, in the range 40%–50% of mean baseline. At week six it had increased to $\sim 60\%$ and in weeks 9 and 10, it had increased to $\sim 130\%$ of baseline.

In the second cat, starting three weeks post-implantation, baseline twitch force measurements were made five times over a period of 10 weeks (Fig. 13). All mean twitch forces in this Fig. were normalized to the mean of these three measurements. Just prior to DC delivery (DC1), the twitch force had increased from the previous two baseline values to a normalized value of 1.3. DC (1 mA for 10 min) was then delivered. No force was detected a week after DC application. The first sign of recovery started three weeks later. Force gradually recovered to the value just before DC1 over the next 13 weeks. A second DC application (1 mA for 9 min) was delivered in week 30 post-implant. Twitches were again abolished, but again gradually recovered over the subsequent 20 weeks.

Fig. 14 shows the results of the first DC application (DC1) on an expanded time scale. Twitch force amplitude was reduced gradually over the 10 min DC was applied. DC application was discontinued once twitches completely disappeared. Force did not recover for the following 54 min.

D. DC Application During Conduction Block With Lidocaine

It has been posited that high-frequency electrical stimulation of nerves damages them by over-activating voltage-gated sodium channels in the neuronal cell membrane [33]. Lidocaine blocks sodium channels [34], the activation of which is required for the generation of action potentials at nodes of Ranvier and therefore the propagation of nerve activity. It was found that when Lidocaine was applied to nerves, this protected them from high-frequency stimulation [35]. We reasoned that if Lidocaine also protected nerves from damage caused by DC, this would

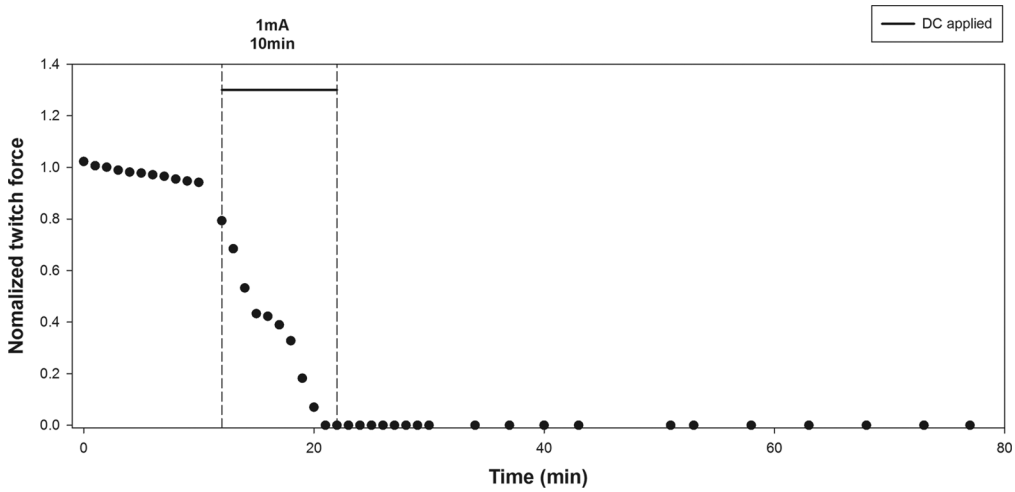

Fig. 14. DC delivery (DC1 of Fig. 13) on an expanded time scale. Mean twitch forces are shown for 10 min prior to DC delivery. DC caused the force gradually to decline over a further period of 10 min. DC was discontinued when twitches disappeared. Force continued to be monitored for a further 54 min to ensure that nerve conduction had been completely blocked.

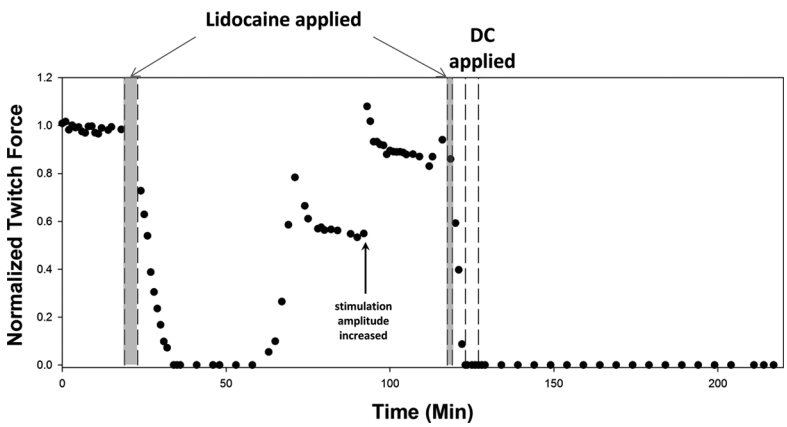

Fig. 15. Lack of neuroprotective action of Lidocaine during DC delivery. Lidocaine was administered twice, the first time (left arrow) to establish the time course of nerve block and recovery, the second time (right arrow) to cause nerve block during DC delivery. First Lidocaine application completely blocked the nerve within 14 min. T_1, the time required for the force to begin to recover from the Lidocaine block was 29 min. At the vertical arrow, the amplitude of the test stimulus pulses was increased, which resulted in an increase in twitch force. Lidocaine was re-administered for a second time and complete conduction block was achieved 5 min later. One minute after this, 3 mA of DC was delivered for 4 min. Force did not recover for the remaining 2 h of monitoring, indicating that Lidocaine had not protected the nerve from damage.

suggest that DC might ablate nerves by over-activating sodium channels.

Accordingly, we performed experiments in two rabbits and one cat to test this hypothesis. Baseline force measurements were made for several minutes (cat experiment, Fig. 15) and then a 1% solution of Lidocaine was slowly injected over 2–4 min into the distal (DC) nerve cuff until muscle twitches started to decline. T_1, the time from complete abolition of twitches to the time twitch forces recovered to 60%–80% of baseline was established. Following the recovery of twitch force, an identical dose of Lidocaine was then applied to the nerve. Once nerve conduction was again blocked, DC (3 mA) was delivered for 4 min. Following this, the nerve was allowed to recover for a time greater than $2 * T_1$. In the three animals, T_1 ranged from 30 to 120 min. In the case shown in Fig. 15, although the test stimuli had been set to $2 * \text{threshold}$ (0.6 mA) prior to Lidocaine blockade, during recovery, a further increase to 0.8 mA was needed. In all three experiments, twitch forces abolished by DC in the second half of the trials did not recover. In the two rabbits, the contralateral leg served as a control, whereby only DC (3 mA for 4 min) was applied, to confirm that at these parameters DC caused long-lasting blockade.

In the cat, to rule out a cumulative effect of repeated Lidocaine blockade, in the contralateral leg, the blockade was performed once and 1 mA of DC was applied during this blockade for 10 min (DC parameters shown to produce ablation (results of experiment not shown)). Force did not recover for the remaining 2 h of monitoring, again indicating that Lidocaine had not protected the nerve from damage.

IV. Discussion

In this study we explored a range of DC amplitudes and durations that provided controlled amounts of nerve ablation. We then demonstrated that DC abolished hyperactive stretch reflexes in the absence of anesthesia in a decerebrate animal model of spasticity. In cats with implanted nerve cuffs we found that nerves could be DC-ablated via a subcutaneous port, that they

recovered over time and that DC ablation was repeatable. Finally, possible mechanisms of DC nerve ablation were explored.

A. Cumulative Effects

The present results confirmed previously reported cumulative effects of DC application. Here we tested DC amplitudes of 0.75 mA and above, applied for relatively short durations. In the anesthetized animals, complete and immediate conduction block was apparent in the majority of DC applications. The only times this did not occur were at the first application, at instances where the DC duration was brief ($<$ 1 min) and where DC amplitude was less than or equal to 1 mA (e.g., Fig. 8).

B. Amplitude or Duration?

In some of the experiments, one of the two parameters (DC amplitude and duration) was increased in successive applications while the other remained constant. Thus, in Fig. 7, DC duration was increased while the amplitude was constant (except for one application). Twitch force did not show a graded attenuation. On the other hand, in Fig. 8, DC amplitude was increased while duration remained constant. A more controlled attenuation was seen. In some of the experiments, graded attenuation was observed after repeated DC applications even though both the DC amplitude and duration were constant. More experiments are required to clarify how best to achieve graded attenuation.

C. Type of Nerve Block

The rapid attenuation of nerve conduction observed during DC in our experiments was presumably due to a "cathodic block" [36] in which a constant depolarization of the membrane prevents action potentials from propagating. In the experiment in the decerebtrate cat, a short period of EMG activity was recorded when DC was turned off (not shown in the figures). This indicates that a virtual anodic block may also have contributed to conduction block.

D. Charge and Charge Density

When alternating current is applied to brain tissue the charge per phase and charge density per phase have been shown to be cofactors in producing nerve damage. [32]. Correlations between these variables and the attenuation of nerve conduction could potentially be useful in predicting outcomes in clinical applications but unfortunately we did not find any systematic correlations.

E. Recovery Between DC Applications

In some but not all successive DC applications, the longer the interval between DC applications, the smaller was the duration of conduction block (and presumably the amount of nerve damage) resulting from a subsequent DC application. In a previous study, longer DC "off" durations resulted in faster nerve recovery from DC block [37]. These results were obtained using a SINE (separate interface nerve electrode), discussed below, which did not produce lasting nerve damage.

F. Regeneration After Ablation

Following nerve damage, the distal part of the nerve undergoes Wallerian degeneration and the proximal nerve portion undergoes "die-back" to the first node of Ranvier [38]. The nerve then starts regenerating toward the denervated muscle. In our study, the first evidence of recovery of muscle force after DC ablation in Cat 2 occurred at 28 and 49 days after DC delivery (Fig. 13). This is comparable to the 38–40 days quoted by Gutmann *et al.* for recovery of muscles after nerve damage in rabbits. Gutmann found that recovery after nerve crush ($\sim$ 3 mm day) was faster than recovery after nerve cut and suture ($\sim$ 2 mm day) [39]. Nerves damaged by DC may therefore be more comparable to nerve crush than nerve cut injuries, though there may also be differences between rabbits and cats. Interestingly, although force production elicited by proximal nerve stimulation in the targeted muscles was abolished in the weeks after nerve ablation in the chronically implanted cat, there were few behavioral signs of this. Gait appeared to be fairly normal, with no obvious reduction in ankle flexion during the swing phase of gait. However, it is known that compensatory movements about the hip and knee develop quickly after nerve injury in cats [40] and this may have masked deficits at the ankle.

G. Could DC Ablation Reduce Spastic Hyperreflexia While Preserving Voluntary Muscle Force?

A complete recovery of twitch force was observed following DC nerve ablation in the chronically implanted cats. In a previous study, three years after cutting the nerve to the triceps surae muscles, muscle force had returned to pre-lesioned values, yet the reflex responses to muscle stretch were greatly attenuated [41]. It was further noted that the reflex attenuation was observed after nerve cut, but not crush. In an earlier study, after a nerve transection and subsequent regeneration, the number of functionally identifiable muscle–spindle and tendon–organ afferents was reduced to 25% and 45% of normal, respectively [42]. In a clinical application, the effect of nerve transection could be to reduce hypertonus, even after muscle fibers are fully reinnervated. Since one of the characteristics of spasticity is overactive stretch reflexes [43], the resulting attenuation of the reflex response without loss of motor control or strength following recovery could be very beneficial. It is not known whether DC ablation has this effect.

H. Mechanisms of DC-Induced Nerve Damage

Electrochemical reactions and reaction products at the electrode–nerve interface have been proposed as nerve-damaging mechanisms [44]. Reactions at the cathode include double-layer charging, oxygen and oxide reduction, H2 evolution, increased pH and the formation of hydrogen peroxide and nascent oxygen. However in one study, Lidocaine or Procaine administered to nerves and blocking conduction in them, protected them from the otherwise damaging effect of charge balanced, high-frequency stimulation [35]. It was concluded that the nerve damage in the absence of local anesthetics was due not to electrochemical reactions, but rather to some biological process (e.g., hyperactivity of the damaged nerves or activation of sympathetic nerve axons, reducing the oxygen supply) which

was suppressed by the local anesthetics. In our experiments, DC abolished muscle twitches, which is inconsistent with nerve hyperactivity. Furthermore, nerves treated with Lidocaine did *not* recover from the application of DC. In Fig. 15, after the initial control Lidocaine application, an increase in stimulation amplitude was needed to restore the twitch forces to pre-Lidocaine baseline values, indicating a persistent effect of the Lidocaine or perhaps of the low-pH saline used to wash out the Lidocaine. It could be argued that the second dose of Lidocaine had an even longer-lasting effect, obscuring an eventual recovery from the DC application. In order to rule this out, Lidocaine was applied only once to the nerve in the contralateral leg of the cat, followed by an application of DC using current and duration parameters previously shown to produce ablation. Lidocaine was not neuroprotective in this experiment either, so the mechanisms suggested by Agnew *et al.* are unlikely to explain DC nerve damage.

It should be noted that at high concentrations, Lidocaine itself can cause nerve damage [45]. In the present study, 1% Lidocaine was injected twice onto nerves. Kroin *et al.* showed that at this concentration, Lidocaine produced temporary nerve blocks but no lasting loss of motor function, even when repeated three times a day for three days. It is therefore unlikely that the lasting conduction block we observed was due to the Lidocaine.

In a recent study DC was delivered to nerves with either a Pt electrode or a stainless steel electrode physically separated from the nerve by a column of 0.9% isotonic saline (separate interface nerve electrode: SINE; [37]). DC delivered with the Pt electrode produced rapid, irreversible nerve damage, whereas DC delivered with the SINE blocked nerve conduction during DC, but conduction recovered quickly after DC ceased. These findings point to a mechanism involving metal–tissue reactions.

In a previous study, color pH indicators showed large increases in pH when DC was delivered in a solution that simulated the electrolytic composition of blood [46]. Mortimer *et al.* suggested that the rate of change of pH was responsible for tissue damage by electrical stimulation and not the change in pH itself [47]. These researchers found that current densities above 50 $\mu\mathrm{A}/\mathrm{mm}^2$ damaged muscle tissue. This is an order of magnitude less than the current densities in our experiments, so the pH changes in our experiments may have been much greater. However, another study [48] showed that pH shifts observed *in vivo* following unbalanced electrical stimulation were smaller than ones measured *in vitro*, probably due to the buffering action of proteins. Results from neurofilament H staining (Ravid *et al.* 2011) showed that nerve damage was localized to an area inside the cuff. It is conceivable that the cuff restricted the spread of alkaline reaction products and those that escaped were physiologically buffered by extracellular fluid. The damage seen within the cuff could thus still have been a result of a large increase in pH. Further pH testing during DC application to peripheral nerves *in vivo* should be conducted in order to determine the true shift in pH that occurs during such stimulation.

Nerve damage at the electrode–tissue interface may persist after the cessation of DC. In Fig. 5 for example, continuing attenuation in force was noted after three of the applications of DC. This was also seen in the experiment of Fig. 9 and in the decerebrate cat (Fig. 12). It is unclear why post-DC attenuation occurred on some occasions but not others.

It is difficult to perform functional muscle tests during DC application to nerves in conscious animals. In order to test whether DC causes enough nerve ablation to reduce spasticity when applied in the absence of anesthesia, we conducted an experiment in which DC was delivered to the tibial nerve of an unanesthetized, decerebrate cat that had developed decerebrate rigidity. The results, presented in Figs. 10–12, showed a complete reduction in force and EMG. This provides initial evidence that DC could reduce spastic hypertonus.

I. Concluding Remarks

Our study showed that nerve ablation with relatively short durations of DC is effective in reducing muscle force in a controlled manner. We were hoping to establish combinations of DC amplitude, duration, charge and charge density that could be used to predict the time course and completeness of nerve ablation. Although nerve damage generally increased with increasing current and duration, the particular way conduction block evolved varied widely from case to case. Although the DC nerve cuffs were placed and tightened on nerves in as similar way as possible between animals, it is likely that the intimacy of contact between the terminals and the nerves varied. In addition, there could be much biological variation in the susceptibility of nerves in different animals to DC-inflicted damage. In clinical applications, small variations in the tightness of nerve cuffs, growth of connective tissue within the cuffs, and slight misalignments between the axes of the electrode terminal and the nerve may occur, resulting in significant differences in the current and duration parameters required to produce a desired amount of partial nerve ablation in different individuals. In the interests of safety, it is therefore likely that a trial-and-error approach similar to the one we adopted in this study would be advisable. Regarding the mechanism of DC nerve ablation, electrochemical reactions and reaction products seem the most likely factors. Before a clinical trial of controlled DC nerve ablation could be considered, potential adverse effects such as pain during DC and the development of neuropathic pain after DC should be evaluated in chronically implanted animals.

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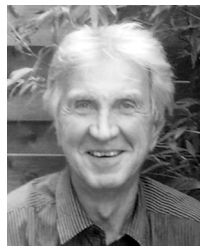

Arthur Prochazka is a Professor in the Centre for Neuroscience, University of Alberta, Edmonton, AB, Canada. His basic research concerns the control of voluntary movement by the nervous system. Clinical projects focus on improving hand function after stroke and spinal cord injury, with the use of muscle stimulators and an exercise workstation, the ReJoyce (Rehabilitation Joystick for Computerized Exercise). Recently the system was used in the first randomized controlled trials of tele-rehabilitation over the internet. It is now used in rehab hospitals in over a dozen countries. Other projects include nerve stimulation and blockade to control bladder function and spasticity, with the use of the StimRouter hybrid implant.