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Characterization of high capacitance electrodes for the application of direct current electrical nerve block

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Abstract

Direct current (DC) can briefly produce a reversible nerve conduction block in acute experiments. However, irreversible reactions at the electrode–tissue interface have prevented its use in both acute and chronic settings. A high capacitance material (platinum black) using a charge-balanced waveform was evaluated to determine whether brief DC block (13 s) could be achieved repeatedly (>100 cycles) without causing acute irreversible reduction in nerve conduction. Electrochemical techniques were used to characterize the electrodes to determine appropriate waveform parameters. In vivo experiments on DC motor conduction block of the rat sciatic nerve were performed to characterize the acute neural response to this novel nerve block system. Complete nerve motor conduction block of the rat sciatic nerve was possible in all experiments, with the block threshold ranging from −0.15 to −3.0 mA. DC pulses were applied for 100 cycles with no nerve conduction reduction in four of the six platinum black electrodes tested. However, two of the six electrodes exhibited irreversible conduction degradation despite charge delivery that was within the initial *Q* (capacitance) value of the electrode. Degradation of material properties occurred in all experiments, pointing to a possible cause of the reduction in nerve conduction in some platinum black experiments.

Keywords

Electrode; Nerve block; Platinum black; Direct current; Nerve damage

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1 Introduction

Many neurological diseases are characterized by unwanted neural activity. Kilohertz frequency alternating current (KHFAC) nerve block (reviewed in Kilgore and Bhadra 2014 [27]) has been widely explored. However, it produces an onset response in the nerve when first turned on and is a deterrent to use in certain applications [8]. The onset response can produce considerable unwanted physiological responses and can last from ~100 ms to many seconds, depending on waveform frequency, amplitude, and electrode geometry/placement [8, 26]. Modification of the KHFAC waveform alone has not eliminated the onset response, but Ackermann et al. [3] demonstrated that the onset response duration could be reduced to a typical value of 2 s with the proper selection of electrode geometry, and frequency. It is possible to completely neutralize the onset response by using a brief DC nerve block through a flanking electrode [4]. However, using conventional platinum electrodes with a DC monophasic waveform resulted in a loss of nerve conduction after only 15 cycles of 2 s each [4]. Our goal in the present paper was to demonstrate that we could repeatedly and reversibly block nerve conduction for a duration of at least 2 s without a reduction in nerve conduction using a modified version of a direct current (DC) block and high capacitance electrodes.

DC nerve block has been used in acute research studies and is reviewed by Bhadra and Kilgore [6]. Historically, it was used for the purpose of blocking larger axons so that small axons could be studied independently [48]. This was studied both in the periphery on the sciatic [12, 37, 45] and in sural nerves [1, 13, 39, 41, 51] as well as in the autonomic system on the vagus [15, 22, 23, 46] and phrenic [40] nerves. This property of DC block was also exploited to demonstrate micturition in the paralyzed bladder [9, 39]. DC has also been used in combination with KHFAC to eliminate the onset response at the initiation of the KHFAC [4, 18]. The DC block needed to mitigate the onset response ranged from 2 to 10 s [4, 18] although 7 s is typical for most instances of KHFAC onset.

Direct current can produce a complete block of nerve conduction. Unlike KHFAC, DC block can be produced without any onset firing by ramping the current from zero to the necessary amplitude for block [25]. Activation at the cessation of DC block (due to anodic break excitation) can also be prevented using a ramped or a decaying phase after the pulse [25, 32, 37, 51]. Unfortunately, DC delivery has previously been demonstrated as unsafe to the nerve (and electrode) for both acute and chronic use [20, 31, 34, 48]. The damage is most likely a result of local pH changes due to oxygen or hydrogen evolution [11]. Changes in pH have been demonstrated to depress the excitability of nerves [24] and cause cell death in neurons and glia [19]. It has been shown by Ackermann et al. [5] that if the reactants can be isolated from the nerve using a saline buffer, the nerve damage can be suppressed.

DC block introduces charge to the nerve using either capacitive or Faradaic reactions depending on the charge intensity. At low levels, the charge is due to capacitive or pseudocapacitive mechanisms. As the level is increased, reversible Faradaic reactions occur such as oxidation formation and reduction and hydrogen plating. However, for long pulses, the reactants may diffuse away from the electrode interface, which would make these reactions no longer reversible. Further increases in levels result in irreversible reactions including electrode corrosion and electrolysis of water. Neural damage due to DC is likely a result of reactive species which are generated during the stimulation cycle due to non-reversible Faradaic reactions [10, 33, 38]. Both the electrode material and the waveform shape must be designed carefully to avoid these reactions. Typical parameters for electrical stimulation use a biphasic charge-balanced waveform with a pulse width below 1 ms.

However, although 7 s will typically be enough to mitigate most KHFAC onset activity, at a maximum, DC delivery might need to be as long as 30 s [8]. Repositioning the electrode was shown to decrease the onset activity [8] as well as changing the electrode geometry [2]. But it is important to be aware of the possibility of longer onsets in situations where the electrode cannot be moved or modified. Shannon presented a model that specified safe stimulation parameters based on charge density of the electrode and the charge per phase [44] which showed that longer pulse widths could be implemented provided that the electrode surface area was increased. According to Shannon's model, for effective DC block for onset mitigation, the electrode would have to be prohibitively large to remain in the safe region. However, this model is based on experimental data using small pulse widths and bare platinum electrodes. Only the geometric surface area is evaluated. Materials with different roughness factors are not included. A more complete model of acceptable stimulation levels is needed which takes into consideration longer pulses and the unique electrochemistry of different electrode materials.

In order to avoid the generation of any reactive species, it is necessary to fabricate electrodes that have a high enough capacitive/pseudocapacitive charge storage capacity to be able to safely apply prolonged DC for block. The capacitive charge storage arises from the double layer capacitance of the electrode being charged/discharged. The pseudocapacitive region is where there is charge transfer to ions that are directly adsorbed on the electrode surface [34] and no reactive species are produced. The adsorption process has a direct relationship between charge and potential, with the result that it behaves in the same manner as a capacitor, i.e., $Q = \mathrm{CV}$. The metric that is used to describe the capacitive region is the "*Q*" value which is the measured charge in the hydrogen band as measured from a cyclic voltammogram. This value was chosen to restrain the block to a region in which no reactive species are produced to avoid the possibility of damaging the nerve.

For small increases in capacitance, smooth electrodes have been abraded to create a rougher electrode with more effective surface area [43]. However, this is insufficient for the large increases in charge needed for DC nerve block. New electrode chemistries have been studied which increase the effective surface area of an electrode without increasing the geometric area. Platinum black is a material that is fabricated by electroplating platinum on to a smooth platinum electrode under conditions that promote the deposition of a rough, fractal deposit [16, 35, 42]. The use of electroplating allows the electrode to be fabricated/encapsulated and then platinized and replatinized as necessary. This process resulted in electrodes with effective surface areas more than two orders of magnitude larger than bare platinum.

In addition to the electrode material, the waveform shape must be chosen carefully. In order to restore the electrode potential to its original resting value, a biphasic waveform must be used. For capacitive and pseudocapacitive processes, the recharge phase of the waveform must have a total charge that is equal but opposite to the charge of the initial phase [34]. As long as the current passed arises from purely capacitive or pseudocapacitive processes, the electrode potential at the end of a biphasic waveform will return to its original value, and multiple cycles of the waveform can be applied while keeping the range of potentials constant. It should be noted that the charge passed during a cathodic pulse is not completely due to capacitive/pseudocapacitive processes. Because of the oxygenated body fluids, the electrochemical reduction in oxygen to hydrogen peroxide and/or water can occur at the platinum surface. However, due to the high current density of these electrodes, the irreversible charge transfer has been calculated to be <1 % of the total charge, and therefore, complete charge balancing has been employed in all cases [50]. Although total charge balancing is necessary, the level of the current for the recharge does not need to be the same as the current of the initial pulse as long as the total charge is equal. This may be an important design decision depending on the application. The resultant waveform is a charge-balanced, direct current (CBDC) waveform where direct current refers to the mechanism of nerve block.

Although DC nerve block has been utilized to neutralize the onset response from the KHFAC [4], its likelihood of causing nerve damage has prevented any clinical use of DC block. The ability to use DC alone without causing onset makes it a desirable choice for nerve block if the nerve damage can be mitigated. High capacitance electrodes with a CBDC waveform show promise in providing safe DC delivery [18, 47]. The purpose of this study was to demonstrate the feasibility of platinum black electrodes for repeatable direct current nerve block with a duration of at least 2 s.

2 Methods

2.1 Electrode fabrication

Monopolar J-cuff electrodes were fabricated using platinum foil with a platinum wire welded to the contact surface [17]. The platinum wire was a few cm in length and was welded to a stainless steel lead for connection to the instrumentation. This configuration provided a durable lead for connectivity (stainless steel) while keeping the dissimilar metal junction (platinum to stainless steel) away from the tissue. The foil and lead wire were encapsulated in silicone elastomer, and a window was cut on the contact surface to create an interface with the nerve [17]. Rectangular windows were cut to one of three sizes: 3 × 1 mm, 3 × 2 mm or 3 × 3 mm. Electrodes were either left as bare platinum or electrochemically treated to produce high capacitance platinum black electrodes. A total of 23 electrodes were fabricated.

The electrodes were electrochemically cleaned using a square wave of +3 mA for 10 s, −3 mA for 10 s, for 25 cycles in 0.1 M H_2SO_4. The electrode was then electrochemically treated to create a platinum black surface as described in the literature [16]. The platinum black was deposited from a chloroplatinic acid solution [5 g H_2PtCl_6 in 500 ml H_2O, with NaCl (2.9 g) and lead acetate (0.3 g)], and a galvanic square wave (−56 mA/cm^2 “on” current for 5 s, followed by 5 s at open circuit = 10 s/cycle) was applied to platinize the surface. The total charge capacity of the electrode could be controlled through the number of deposition cycles.

The electrochemical water window is defined as the voltage range where neither oxidation nor reduction of water or protons occurs [21]. This metric is used to determine the range at which the electrode can be operated without creating electrochemical products that are damaging to the tissue. To analyze the water window, a cyclic voltammogram [21] for each of the electrodes was generated using a Solartron Inc., Model 1280B potentiostat using a BASi RE5B reference electrode (measurements are accurate to within 10 mV) with sweep rate 10 mV/s, voltage range of − 0.225 to +1.20 V, and sampled at 10 Hz. For platinum and platinum black, the amount of charge that could be safely delivered by these electrodes (referred to as the "*Q* value") was estimated by calculating the pseudocapacitive charge associated with hydrogen adsorption by integrating between −0.25 and +0.15 V, as shown in Fig. 1. This voltage range represents the region in which hydrogen adsorption occurs. The integration was performed relative to a baseline current equal to the double layer charging current [49]. This procedure provides a conservative estimate of the *Q* value for each electrode, as the double layer charging capacity, which represents roughly 10 % of the total capacity, has been not been included in the reported *Q* value. The charges associated with adsorption (cathodic currents) and desorption (anodic currents) were separately calculated and averaged to determine the *Q* value. Although the anodic and cathodic charges should be the same, in practice the calculated values are seldom exactly equal, and as a result the average was taken.

2.2 In vitro electrode testing

Platinum black electrodes were electrochemically cleaned and tested in vitro after each in vivo experiment to determine how much the *Q* value degraded during the in vivo experiment. If the post experiment *Q* value was >19.0 mC, the electrode was reused. To perform cycles of at least 1.6 mC with a 4/7/2 waveform, a 16-mC *Q* value would be needed. In order to be sure to block at <85 % of the *Q* value, 19.0 mC was chosen as a minimum value. If the *Q* value was below 19.0 mC, the surface was renewed by reapplication of platinum electrochemically. This resulted in different electrode "configurations" which consisted of an existing physical electrode with a new *Q* value. The new *Q* value was either the result of re-coating the electrode or the result of degradation of the electrode surface caused by adsorption of proteins on the surface and mechanical manipulation of the electrode.

A total of 80 platinum black electrode configurations were generated by either initial platinization or replatinization.

Several in vitro tests were performed to analyze the stability of the *Q* value. An in vitro cumulative charge test was performed in sulfuric acid where a test pulse of 10-s cathodic at 67 % of the *Q* value was applied and then a 100-s recharge at 10 % of the cathodic amplitude was applied. This test pulse was cycled 100 times, and then the *Q* value was tested. The cycles were stopped when the *Q* value of the electrode dropped below 67 % of the original *Q* value. Finally, since the electrodes are curled around a rod after coating to form the cuff electrode, the mechanical stability of the electrode during curling was tested in vitro. The *Q* value was recorded, and then the electrode was curled 180 degrees around a piece of solid copper wire (diameter = 0.040″ = 1 mm). After each curl, the electrode was uncurled and the *Q* value was retested. This simulates the mechanical stresses that the electrode experiences during the in vivo testing when it is placed on the nerve.

2.3 In vivo test setup

Acute experiments were performed on Sprague–Dawley rats to test the efficacy of CBDC nerve block with the high capacitance electrodes. All experiments were approved by our institutional animal usage committee. The surgical setup has been described previously in [7]. Under anesthesia (Pentobarbital intraperitoneally), the sciatic nerve and the gastrocnemius muscle on one side of the animal were dissected. The Achilles tendon was severed from its distal attachment. The tendon was then attached to a force transducer (Entran, Fairfield, NJ; resolution 0.005N) to measure forces due to muscle twitches (Fig. 2).

Three electrodes were placed on the sciatic nerve. The two stimulating electrodes [proximal stimulation (PS) and distal stimulation (DS)] were used to test the efficacy of the nerve block and the integrity of nerve conduction. The stimulating electrodes were bipolar J-cuff electrodes and are described in detail in [17]. The stimulating electrodes were connected to a Grass S88 stimulator (Grass Technologies, West Warwick, RI, USA) with a current-controlled output. The stimulation waveforms consisted of a 20-μs supramaximal cathodic pulse (typically 0.5–1.0 mA) at 1 Hz for the proximal electrode and 2 Hz for the distal electrode. The amplitude of the stimulus was chosen to produce full muscle recruitment of the gastrocnemius-soleus muscle [6].

The CBDC electrode was placed around the sciatic nerve between the two stimulating electrodes. The CBDC electrode was connected to a current-controlled waveform generator (KI-6221 Keithley Instruments, Solon, Ohio) with a subcutaneous needle for the return. The CBDC waveform consisted of a cathodic phase (producing nerve block) and an anodic recharge phase as shown in Fig. 3. The cathodic phase consisted of a ramp-to-plateau phase, a plateau phase, and a ramp-to-recharge phase. The slope of the ramp-to-plateau and ramp-to-recharge phases was adjusted so that these transition phases did not produce any neural activation [1, 37]. The total charge delivered in the cathodic phase was always less than the *Q* value for that particular platinum black electrode. The total charge is calculated by integrating the entire cathodic phase. Since the *Q* value for platinum is several orders of magnitude less than platinum black, when platinum electrodes were tested, the total charge delivered was outside the *Q* value for the electrode. The duration of the recharge phase was selected to balance 100 % of the charge at a current level of 10 % of the cathodic plateau level.

A complete conduction block of the motor fibers in the sciatic nerve was demonstrated by measuring the force produced by stimulation through the proximal electrode. When the cathodic plateau was sufficient to block all motor action potentials generated by the PS electrode, the gastrocnemius peak force was reduced to zero. The nerve was considered to be “completely blocked” at this cathodic amplitude (Fig. 3).

2.4 Block threshold experiments

The smallest cathodic amplitude that produced a complete block of gastrocnemius force (as shown in Fig. 3) was defined as the "block threshold." Block threshold testing was initiated using a cathodic waveform with a total charge set to 50 % of the *Q* value of the electrode being tested. The amplitude was then increased or decreased until the block threshold was found using a binary search pattern with a block threshold resolution of 0.1 mA. The total charge was calculated in each test to ensure it did not exceed 90 % of the *Q* value. Typically the plateau phase was set to 2 s and the ramps were set to 2 s. However, if activation occurred during the ramp phase, the length of the ramp was increased until no activation occurred. If it was difficult to determine whether the signal was completely blocked during the plateau, the plateau duration was increased. CBDC block thresholds were determined for 80 different platinum black electrode configurations.

In order to determine whether the *Q* value or the electrode size had an effect on the block threshold, a two-way ANOVA was performed on the block threshold data. The independent variables were the width of the electrode, the *Q* value before the experiment, and the *Q* value after the experiment. The dependent variable was the block threshold.

2.5 Nerve conductivity experiments

The PS and DS electrodes were used to monitor the integrity of nerve conduction over the duration of the experiment. At the start of the experiment, the force resulting from stimulation of each of these electrodes was determined and the ratio of the peak twitch force from the proximal stimulation (PS) to the peak twitch force from the distal stimulation (DS) was recorded (referred to as the "PS/DS ratio"). For a healthy nerve, the PS and DS should produce muscle twitches that were equal in magnitude, making the PS/DS ratio close to one. The result of PS and DS stimulation is illustrated in Fig. 3. If the conductivity of the nerve was compromised under the CBDC electrode, the PS/DS ratio would drop below the ratio recorded at the start of the experiment. This ratio was recorded periodically during the experiment to monitor nerve conduction. The normalized PS/DS was calculated by dividing each PS/DS ratio by the initial PS/DS ratio recorded during the experiment. The value of the PS/DS ratio as an evaluation of nerve health is that the health of the nerve can be evaluated in real time during the experiment. Unlike histology, which can only be performed after the damage has already been done, the PS/DS ratio can show the progression of the damage over time to allow an estimate of the point at which the damage occurred.

A waveform protocol was chosen where the plateau would need to be long enough to block the onset from KHFAC block. A plateau of 7 s was determined to be sufficient for most instances of KHFAC onset. A 4-s ramp-to-plateau phase was chosen as a worst case estimate for the maximum time needed to prevent onset due to DC. The CBDC waveform protocol typically consisted of a 4-s ramp to DC, 7s plateau, and 2-s ramp to recharge. However, in some trials the ramp times needed to be increased in order to prevent onset activity. In these trials, it was necessary to decrease the plateau time in order to stay within the water window for the chosen plateau current.

At the start of each experiment, a PS/DS ratio was recorded followed by a block threshold measurement. Using the DC waveform generator, CBDC waveforms were repeatedly delivered to the nerve. The PS/DS ratio was recorded after every 10–20 repetitions to evaluate nerve health. At the beginning of each multi-cycle trial, proximal stimulation was applied to demonstrate that complete block was still being produced during the CBDC plateau. This procedure was repeated until one of three terminal events occurred: (1) 100 CBDC cycles were applied, (2) the PS/DS ratio dropped below 0.5, or (3) the animal expired. In three experiments, the PS/DS ratio was still above 0.9 after 100 cycles and the animal was still responding well to the procedure, so the experiment was extended beyond 100 cycles.

An electrode test was defined as a "Pass" if the PS/DS ratio at the end of the experiment was above 0.90, "Fail" if below 0.5, and "Partial if between 0.5 and 0.90. For bare platinum, four nerve conductivity experiments were performed in three animals, and for platinum black, six nerve conductivity experiments were performed in six animals. In order to eliminate the geometric size as a source of variation, all electrodes were 3 mm × 2 mm.

3 Results

3.1 In vitro test results

Results for in vitro testing are shown in Fig. 4. In vitro cumulative charge testing shows that the application of charge causes the Q value to decrease. The Q value decreased to <67 % of the starting Q value within 200–500 cycles. Curling the electrode also causes the Q value to decrease. After just 10 bends, the Q value is half of the starting Q value.

3.2 Block threshold results

In all 80 platinum black experiments, it was possible to find a DC plateau that caused complete block. Figure 5 shows the block threshold versus the starting Q value for the electrode for each of the electrode sizes. Following an ANOVA test, the p values for Q before, Q after, and electrode width were 0.52, 0.87, and 0.75, respectively, indicating no significant effect on the block threshold from these variables.

The median block thresholds for each size of electrode were −0.85 mA for 1 mm, −0.9 for 2 mm and −1.55 for 3 mm. The ranges of block thresholds were −0.15 to −2.90 mA for 1 mm, −0.2 to −3.00 for 2 mm, and −0.50 to −2.20 mA for 3 mm. Q value ranges for each size of electrodes were 2.4–10.1 mC for 1 mm, 6.3–36.0 mC for 2 mm, and 20.0–32.4 mC for 3 mm.

3.3 Nerve conductivity experiments results

Ten nerve conductivity experiments were performed: four using bare platinum electrodes and six using platinum black electrodes. The waveform parameters, block thresholds, and outcomes are summarized in Table 1. For experiment "Pt Black 1," the tested plateau was below the block threshold for the electrode. For all other experiments, the tested plateau value was equal to or above the block threshold for the electrode. For all electrodes that were tested at plateau values above the block threshold, complete block was achieved for all cycles of the experiment. The total DC time refers to the total time for both the cathodic pulse and the anodic pulse accumulated over all cycles. The *Q* values for the electrodes are summarized in Table 1. For the platinum black electrodes, the total charge of the cathodic phase was always below “*Q* start” for the electrode.

Results for the nerve conductivity experiments are shown in Figs. 6 and 7. In four experiments, a conduction failure occurred where the PS/DS ratio fell below 0.5 (Fig. 6). Three of these used bare platinum electrodes (Bare Pt 1, 3, 4), and one used platinum black electrodes (Pt Black 6). In two experiments, the PS/DS ratio was reduced by more than 10 %, but not below 50 % (Fig. 6, Bare Pt 2, and Pt Black 4).

Four platinum black electrodes exhibited no significant decrement in the PS/DS ratio and were considered “Passes.” The results for these four electrodes are shown in Fig. 7. The total cumulative charge ranged from −2126 to −3326 mC with a total DC delivery time (including recharge) of 136.7–376.7 min. The total time of complete block as defined as DC amplitude exceeding the block threshold ranged from 2.7 to 43.3 min with one trial that did not reach block threshold using the defined plateau value. The cathodic plateau amplitude for the passes spanned the entire range tested for the platinum black electrodes (−1.6 to −3.0 mA) and the percentage of the starting *Q* value also spanned the entire range tested (53–97 %). Thus, there was no obvious direct link between the electrodes that passed and either the plateau amplitude or the percentage of *Q* value utilized. Four of the six platinum black electrodes passed our criteria, and in two cases, we were able to repeatedly apply a 7-s block (with a 100-s recharge) for a total of 200 consecutive cycles with instant reversibility maintained throughout the entire test period (total experiment duration ~8 h).

3.4 Electrochemical results

After each experiment, the electrode was cleaned and the *Q* value was retested. The *Q* start and *Q* final are displayed in Fig. 8 for 62 experiments using platinum black electrodes with widths of 1, 2, and 3 mm. A linear fit line indicates a larger degradation of the *Q* value for electrodes with larger *Q* values for all electrode sizes. Comparison of R^2 values shows that wider electrodes have more variability in the change of the *Q* value.

4 Discussion

These experiments demonstrate that platinum black electrodes can acutely provide repeated, reversible complete CBDC block. In these experiments, we delivered DC block for a cumulated total time of up to 43.3 min without causing a reduction in the conduction of the nerve. In contrast, previous experiments by Ackermann et al. [4] observed irreversible conduction failure with 0.5–1.0 min of cumulative DC block delivery. Thus, the CBDC waveform delivered through high *Q* electrodes was able to extend the cumulative reversible block by greater than one order of magnitude. However, in our experiments, one platinum black electrode failed to meet this criteria and one platinum black electrode exhibited a partial failure. Taken together, these results indicate that operation within the water window is an essential, but not the only, factor critical for long-term use of DC nerve block. Identification of additional essential factors will require further research and is discussed in the paragraphs that follow.

In all experiments, it was possible to provide complete block using the platinum black electrode. However, for Pt Black 1, using the block threshold would have caused the charge delivery to exceed the *Q* value of the electrode, and therefore, it was tested at −1.6 mA. The block was tested at the beginning of each set of cycles and complete block was achieved throughout the experiment for all electrodes except for Pt Black 1. However, it is not known whether the block threshold shifts during the experiment. Evaluating the block threshold throughout the experiment would have required additional cycles of block at varying current levels, complicating the analysis of nerve response to consistent current amplitudes.

A key design consideration regarding the successful use of the CBDC waveform is the relationship between the surface area of the electrode and the current amplitude necessary to block. In the case of the platinum black electrodes, larger *Q* values are obtained by increasing the effective surface area of the electrode. If the block threshold were also found to scale with increasing effective surface area, then it might not have been possible to find a combination of electrode *Q* value and block threshold amplitude that allowed the desired minimum block time of 2 s. However, as shown in Fig. 5, the block threshold is not correlated with effective surface area and is only weakly correlated with geometric surface area (for the ranges tested). The impact of these results is that significant increases in the duration of DC block can be obtained by fabricating electrodes with very large *Q* values. In this study, we fabricated electrodes with *Q* values up to 36 mC. In fact, in one case, a 2-mm-wide electrode with a *Q* value of 36 mC had a block threshold of −0.6 mA, which would have allowed for a block plateau approaching one minute while still remaining within the water window for that electrode. Although such an extreme example may be difficult to achieve consistently, our results do show that it should be possible to consistently achieve our desired target of 2 s of repeatable, reversible nerve block. All of the platinum black electrodes used in the nerve conductivity experiments had a *Q* value of at least 19.6 mC. Using 90 % of this *Q* value as an upper limit for preventing excursion into the water window, this would allow for a CBDC plateau of at least 2.2 mA (assuming a worst case 10-s ramp-to-plateau phase), which would be adequate to achieve complete block for 96 % of the electrodes tested.

The relationship between the four platinum black electrodes that passed our criteria and the two platinum black electrodes that did not pass is difficult to determine. We had expected that the reversibility would be directly related to the percentage of the starting *Q* value over which the electrode was operated. However, for the electrodes that passed, this parameter ranged from 53 to 82 %; and for the electrodes that did not pass, this parameter ranged from 64 to 74 %. In addition, there was no trend in the total charge delivered during the cathodic phase between electrodes that passed and those that did not (16–21 mC for the passing electrodes; 20 mC for the non-passing electrodes).

In vitro testing shows that the degradation of the *Q* value can be attributed to several different conditions. The effect of cumulative charge on the electrode causes the *Q* value to drop by more than half for large cycle times. However, for the limited number of cycles performed for the in vivo tests, it is unclear if this is a factor. However, curling the electrode causes a clear drop of the *Q* value even after just a few curls. In order to place the electrode around the nerve, the electrode is curled at least once and may undergo additional curling if the initial placement of the electrode is not optimal. The decrease in the *Q* value after each curl was variable, and this might explain why some of the electrodes failed while others passed.

The *Q* value measured at the end of the experiment was always lower than the starting *Q* value (range 17–58 % decrease). This can be attributed to mechanical manipulation of the electrode as well as the deposition of proteins on the surface of the electrode. It was not possible to safely perform a cyclic voltammogram in vivo, and therefore, we do not know the time course of the decrease in the *Q* value. The timing of when the degradation in *Q* value occurred could have influenced the success of the platinum black electrodes. In 5 of the 6 platinum black experiments, the cathodic phase charge exceeded the *Q* value measured after the experiment (range 89–195 % cathodic phase charge/*Q* final). However, there was no correlation between this percentage and the amount of conduction reduction that occurred. It is feasible that, in the case of the electrodes that passed, the changes in *Q* occurred near the end of the experiment or during the removal of the electrode from the nerve. We expected that exceeding the *Q* value would cause irreversible conduction failure to occur, but further evaluation of this hypothesis may require a protocol for measuring the *Q* value in vivo. Cogan et al. [14] successfully measured cyclic voltammetry in vivo using iridium oxide electrodes in the subretinal space, although no metrics of nerve damage were assessed. We attempted cyclic voltammogram measurements in vivo with the platinum black electrodes, but we observed significant muscle contraction during the measurement and an immediate, irreversible, decrement in muscle force following the measurement. Better measurement techniques will need to be developed if the *Q* value is to be tracked in vivo.

In these experiments, we utilized a range of CBDC plateau values, from −1.6 to −3.0 mA, and a range of plateau durations, from 2 to 7 s. There was no clear relationship between these parameters and the electrodes that passed or failed. Pt black 3, which passed, had the highest current amplitude of −3.0 mA, but also had the shortest plateau duration of 2 s. Franke et al. [18] used a similar range of CBDC plateaus (−1.7 to −2.5 mA), although the plateau duration was shorter than utilized here (range of 1.0–3.0 s). None of the electrodes in Franke et al. [32] exhibited irreversible conduction failure. These results suggest that a longer duration of current delivery may influence nerve response, irrespective of the total charge delivered. In addition, the plateau amplitude in the failed electrode had the highest percentage of block threshold (286 %), which may indicate that irreversibility is due, at least in part, to the block effect rather than to the electrochemical reactions alone. The relationship between the block parameters and electrode parameters appears complex, and a more systematic assessment of each parameter will need to be performed in order to determine the existence and nature of these relationships.

There was significant variability in the DC block threshold obtained across the 80 electrodes tested (range of −0.15 to −3.0 mA). Although some variation is to be expected based on the variation observed in electrical stimulation thresholds [28], variability that exceeded an order of magnitude was unexpected. Possible causes of this variability include variation in the direct contact between electrode surface and the nerve and the health of the nerve after surgical exposure. In the future, it may be necessary to carefully control the electrode– nerve interface to obtain more repeatable block thresholds. Chronic implantation of the electrodes, allowing encapsulation of the electrode around the nerve, should also demonstrate improved consistency in block threshold value.

We tested four bare platinum electrodes, and in all but one experiment, the electrodes failed completely between −118.0 and −821.4 mC of charge delivery. In "Bare Pt 2," the PS/DS ratio was at 0.72 after −1455.6 mC of delivery and thus was considered a partial fail. It is possible that additional CBDC cycles would have resulted in complete failure on this electrode as well. This latter electrode may indicate that the addition of the recharge phase that is part of the CBDC waveform may serve to extend the working range of an electrode even when the charge delivery is well outside the *Q* value of the electrode (typically 0.035 mC for bare platinum). By contrast, Ackermann et al. [4] used DC block without the recharge phase and observed rapid irreversible nerve damage in all platinum electrodes subjected to DC.

Platinum black was selected for these electrodes for its ease of fabrication and the ability to fabricate electrodes with high *Q* values for testing. Although thin film fabrication techniques have been used to generate high surface area platinum electrodes [29, 30, 36], electroplating on platinum foil was used in this study as it was more amenable to our fabrication techniques. Our electrode fabrication procedure includes heating and compression of the electrode assembly [17], and therefore, it was necessary to use a process that could be applied after the electrode was fabricated. However, the mechanical stability of platinum black is unlikely to be sufficient for chronic implantation, as demonstrated by the degradation in *Q* value over the relatively brief duration of our experiments (Fig. 8). More robust materials that can also provide high levels of capacitance (e.g., IrO_2) could be employed in future studies to develop design techniques for CBDC electrodes. These materials would also be needed in order to demonstrate the feasibility of CBDC in a long-term chronic experiment.

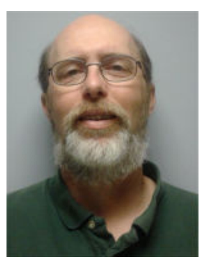
5 Conclusions

High capacitance electrodes in combination with a CBDC waveform show promise as a solution for DC nerve block. Platinum black electrodes were fabricated to demonstrate the feasibility of this approach. Complete nerve motor conduction block of the rat sciatic nerve was possible in all experiments, and the block threshold did not seem to be effected by the increase in *Q* value. It was possible to apply repetitive cycles of CBDC block while still maintaining reversibility in more than half of the platinum black electrodes tested. However, irreversible conduction degradation was shown in several experiments despite charge delivery that was within the initial *Q* value of the electrode. Degradation of the *Q* value that occurs during implantation is one possible mechanism for these failures. Measurement of *Q* values after the experiment show a decrease in *Q* value in all electrodes, indicating that improvement in material properties is likely to be required prior to evaluating this approach chronically.

Biography

Tina Vrabec received the BS and MS degree in Electrical Engineering from Case Western Reserve University, Cleveland, in 1990 and 1995. She spent 7 years working in industry designing firmware for Bailey Controls and Rockwell automation and then spent another 10 years designing software and firmware for medical implants for the Cleveland FES Center. She is currently a researcher working on her Ph.D. in the use of direct current waveforms for nerve block. Her research inter ests include the use of direct current by itself and in combination with kilohertz frequency alternating current (KHFAC) nerve block to provide therapies in both the peripheral and autonomic nervous systems.

Niloy Bhadra received the MBBS and MS (Orthopedics) degrees from Calcutta University, India, in 1982 and 1985, respectively. He became a Fellow of the Royal College of Surgeons, Edinburgh, UK, in 1989. After a career as an Orthopedic Surgeon, he became a Biomedical Engineer, obtaining his MS and Ph.D. from Case Western Reserve University, Cleveland, Ohio, in 2000 and 2005, respectively. His initial research was in the implementation of neuroprosthetic systems in individuals with spinal cord injury (SCI). From 2000, he has been working on electrical methods of producing nerve conduction block and has wide experience in kilohertz frequency alternating current (KHFAC) nerve block and in direct current block. This encompasses computer simulations of nerve block in a mammalian axon model and extensive experimental experience of nerve block in multiple animal models.



Dr. Jesse Wainright is a Research Associate Professor in the Department of Chemical Engineering at Case Western Reserve University. He received his Ph.D. from CWRU in 1992. His research focuses on electrochemical power sources—fuel cells, batteries and supercapacitors. All aspects of these devices are considered: from high-level system models to development of new electrolytes and catalysts, and fundamental studies of proton conduction and oxygen reduction. He has authored or co-authored over 50 papers relating to electrochemistry and electrochemical engineering. His current research interests are the development of implantable electrodes for neural stimulation and nerve block, and novel stack designs and chemistries for PEM fuel cells and redox flow batteries.

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Manfred Franke received the Dipl.-Ing. (MS) degree in Electrical Engineering from the Technical University TU Dresden, Germany, in 2007, and the Ph.D. in Biomedical Engineering from Case Western Reserve University, Cleveland, OH, in 2014. He is a recipient of the Fulbright Fellowship Award and the Doctoral Excellence Award from the Case Western Reserve School of Medicine, the Klinggraeff-Medal and the Friedrich-Naumann-Fellowship. His research interest is the selective activation and inhibition of nerve conduction using electrical and other non-pharmaceutical pathways. His current work at

Oculeve Inc. (acquired by Allergan in July of 2015) focuses on the activation of neural pathways to initiate the secretion of tears and the release of specific tear components for patients suffering from Dry Eye Disease and Blepharitis.

Kevin Kilgore, Ph.D. received the BS degree in Biomedical Engineering from the University of Iowa, Iowa City, in 1983, and the MS and Ph.D. degrees in Biomedical Engineering from Case Western Reserve University, Cleveland, in 1987 and 1991. He is currently Professor, Department of Orthopaedics at MetroHealth Medical Center and School of Medicine, Case Western Reserve University. He is also a Biomedical Engineer in the Research Service of the Louis Stokes Cleveland Veterans Affairs Medical Center and is an Associate Director in the Cleveland Functional Electrical Stimulation Center. His research interests are in the clinical applications of functional electrical stimulation to provide hand and arm function for individuals with paralysis, and in the application of electrical currents to control unwanted neural activity.

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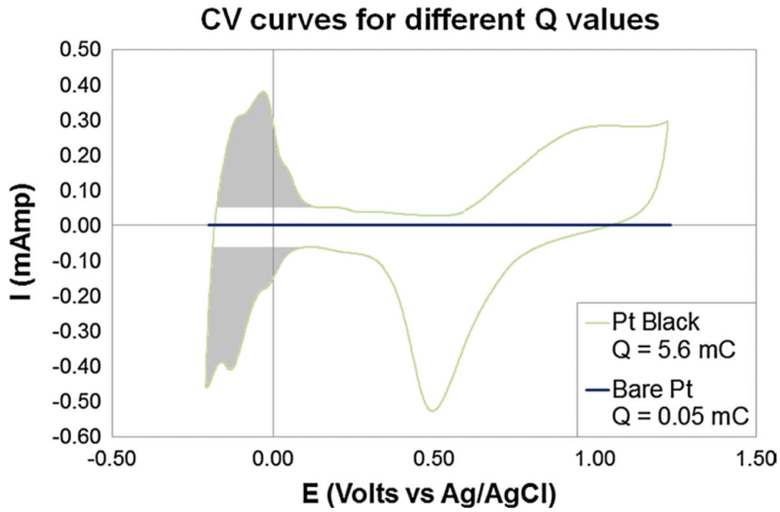

Fig. 1.

Shaded area indicates region used to calculate *Q* value for a given electrode. Total charge was determined by integrating over this region

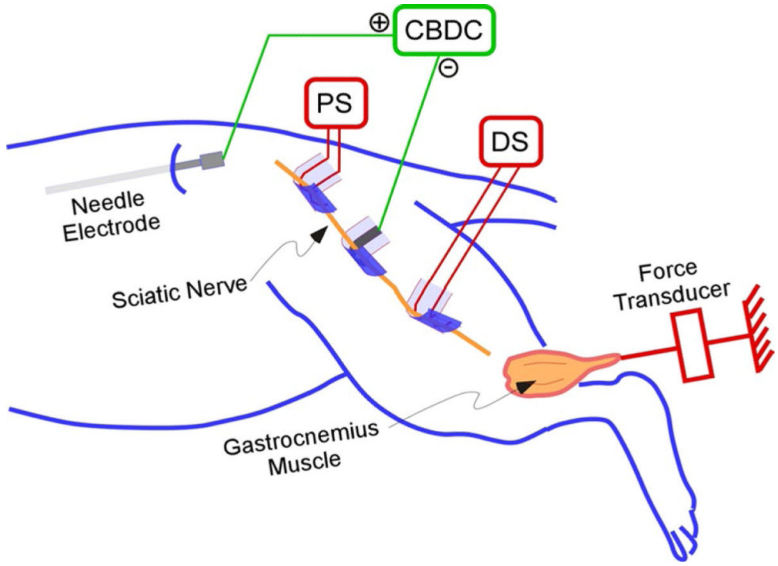

Fig. 2.

In vivo setup for testing characteristics of nerve block electrodes. Blocking electrode was placed between two stimulating electrodes on the rat sciatic nerve (*PS* proximal electrode and *DS* distal electrode). Force from the gastrocnemius muscle was measured to determine block

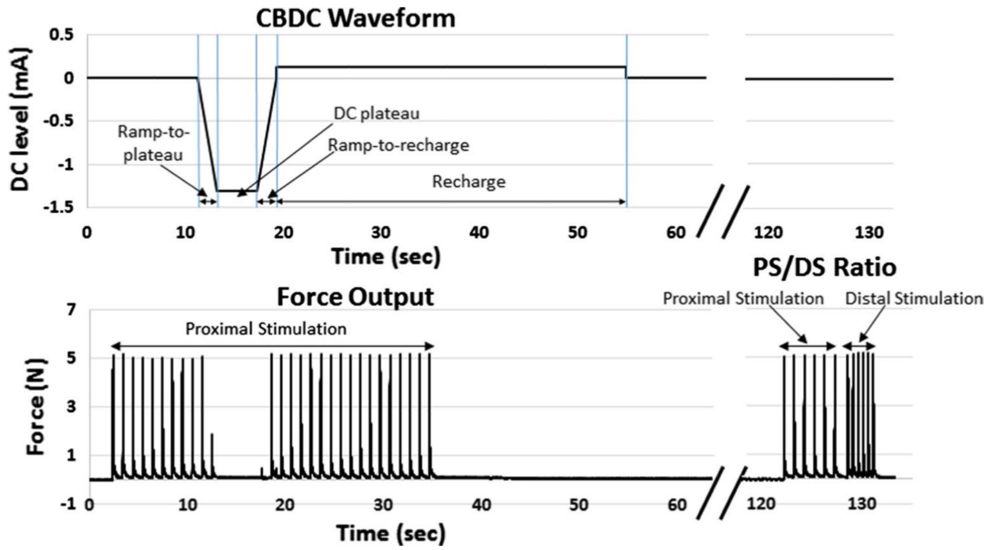

Fig. 3.

DC waveform delivered and resulting force output. Complete block occurs where the force output goes to zero. Ramp-to-plateau and ramp-to-recharge phases were 2 s, and the DC plateau was 4 s. Proximal and distal stimulation are compared after block has completed

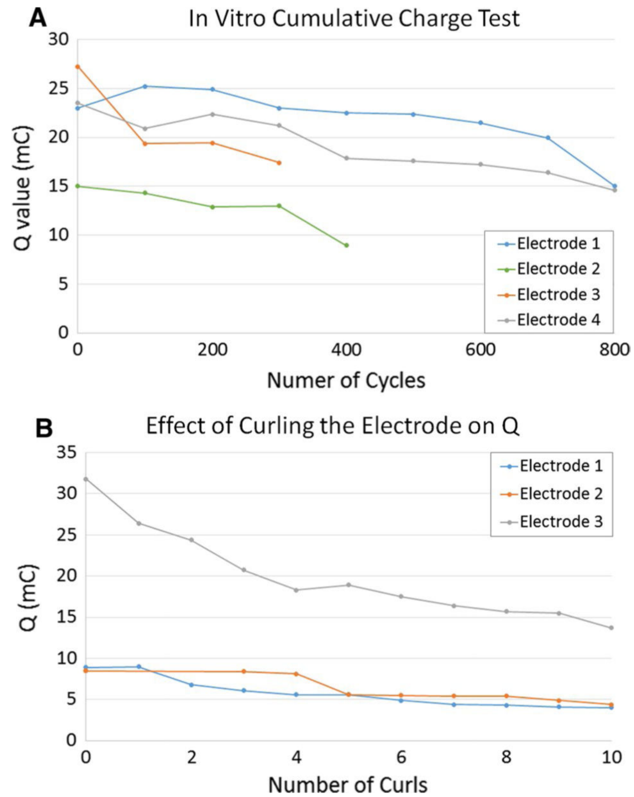

Fig. 4.

Results of in vitro electrode testing. High cycle in vitro cumulative charge is shown in graph (**a**). The effect of bending the electrode is shown in graph (**b**)

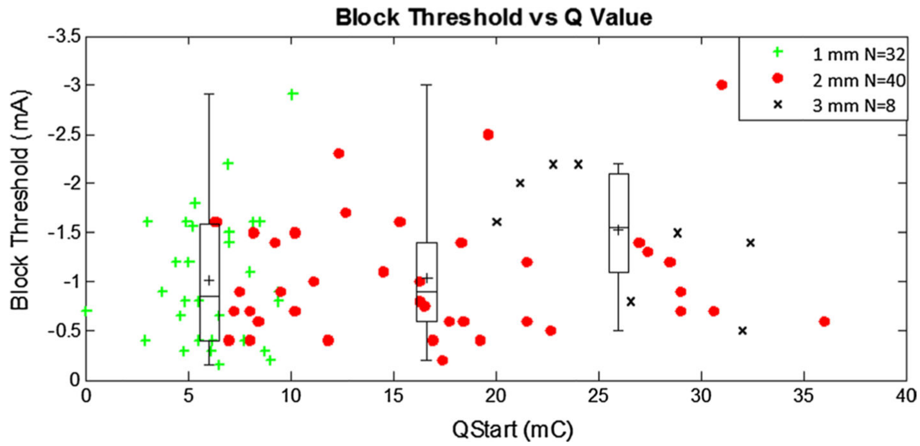

Fig. 5.

Distribution of block thresholds versus *Q* values for three electrode sizes. *Box plots* represent each electrode size increasing from 1 to 3 mm from *left* to *right*. All electrodes displayed are platinum black electrodes. Block threshold is not influenced by the *Q* value

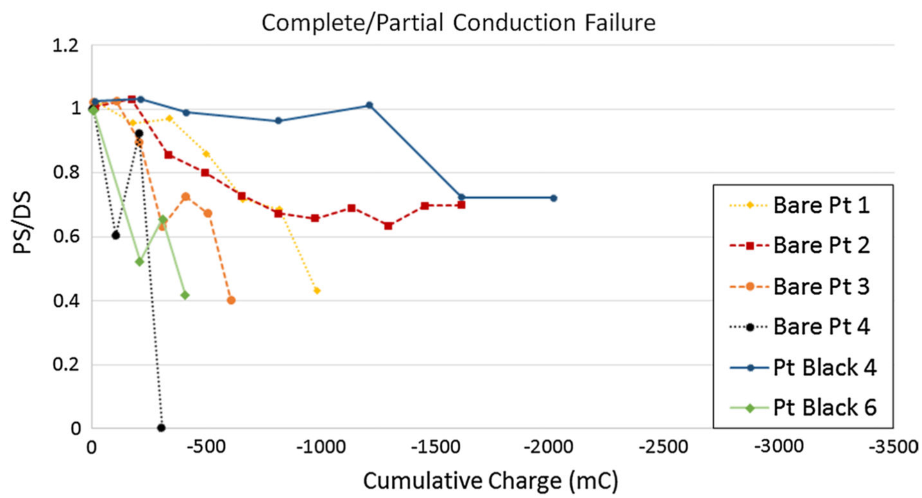

Fig. 6.

Results for the nerve conductivity experiments where conduction failure (PS/DS < 0.5), or partial failure (0.9 < PS/DS > 0.5) occurred. Bare Pt 1, 3, 4, and Pt Black 6 resulted in conduction failure. Bare Pt 2 and Pt Black 4 resulted in partial conduction failure. Cumulative charge is determined by summing the charge in each cycle delivered over time

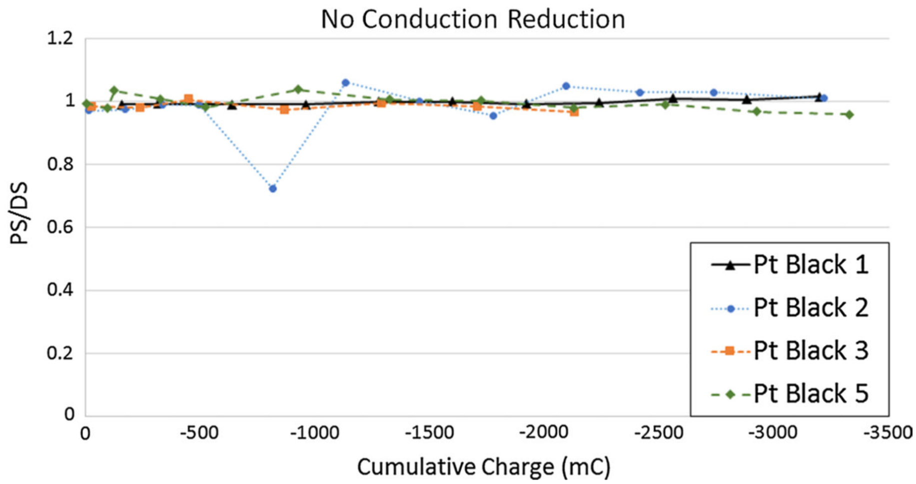

Fig. 7.

Results for the nerve conductivity experiments where no conduction reduction occurred. All electrodes were platinum black electrodes. Cumulative charge is determined by summing the charge in each cycle delivered over time

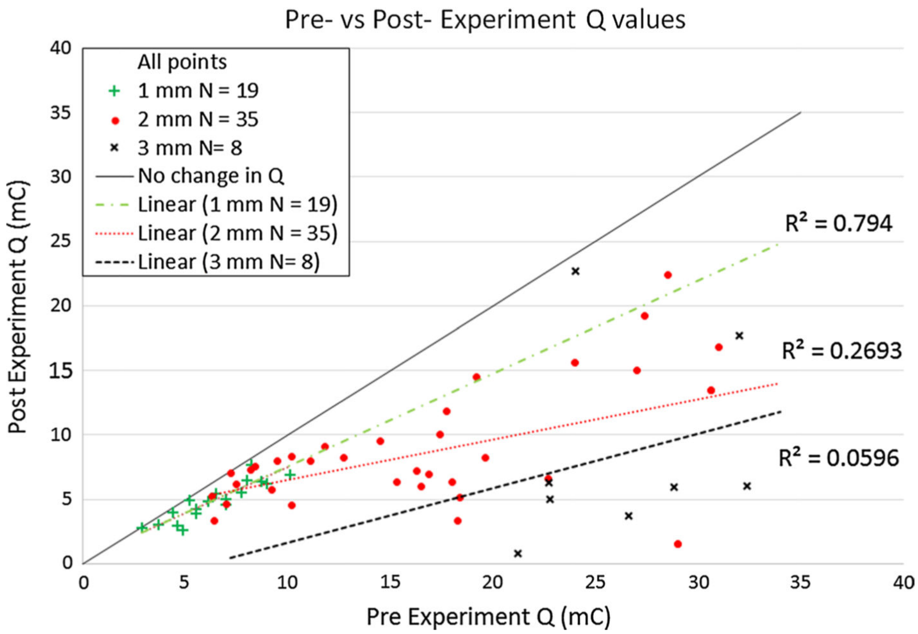

Fig. 8.

Change in the *Q* value as measured at the start and end of the experiment. Trend lines show an increase in *Q* value degradation for all electrode sizes

Table 1

Waveform and electrode parameters and outcomes for cumulative charge tests

Electrode	BT (mA)	Plateau (mA)	Plateau/BT (%)	Ramp to DC (s)	Plateau (s)	Ramp to RC (s)	Number of cycles	Total DC time	Total time above BT	*Q* start (mC)	*Q* after (mC)	% Change in *Q*	% of *Q* start delivered per cycle	% of *Q* after delivered per cycle	Outcome
Bare Pt 1	–1	–1.6	160	4	7	2	60	6780	645	n/a	n/a	n/a	n/a	n/a	Fail
Bare Pt 2	–1.3	–1.6	123	4	7	2	100	11,300	1188	n/a	n/a	n/a	n/a	n/a	Partial
Bare Pt 3	–0.9	–2	222	4	7	2	30	3390	291	n/a	n/a	n/a	n/a	n/a	Fail
Bare Pt 4	–1.2	–2	167	4	7	2	15	1695	159	n/a	n/a	n/a	n/a	n/a	Fail
Pt Black 1	–2.5	–1.6	64	4	7	2	200	22,600	0	19.6	8.2	–58	82	195	Pass
Pt Black 2	–1.6	–1.6	100	4	7	2	200	22600	2600	30	14.6	–51	53	110	Pass
Pt Black 3	–3	–3	100	8	2	2	100	8200	1200	31	16.8	–46	68	125	Pass
Pt Black 4	–1.4	–2	143	4	7	2	100	11,300	1120	27	16.8	–38	74	119	Partial
Pt Black 5	–1.2	–2	167	10	4	2	175	20,300	1960	27.7	22.4	–19	72	89	Pass
Pt Black 6	–0.7	–2	286	4	7	2	20	2260	182	31.1	13.5[a]	–57	64	148	Fail

[a]In addition to the Pt Black 6 experiment, 21 additional cycles of CBDC were performed using this electrode in a separate experiment prior to recording this value