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Electrical neurostimulation with imbalanced waveform mitigates dissolution of platinum electrodes

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Abstract

Objective—Electrical neurostimulation has traditionally been limited to the use of charge-balanced waveforms. Charge-imbalanced and monophasic waveforms are not used to deliver clinical therapy, because it is believed that these stimulation paradigms may generate noxious electrochemical species that cause tissue damage.

Approach—In this study, we investigated the dissolution of platinum as one of such irreversible reactions over a range of charge densities up to $160 \mu\text{C cm}^{-2}$ with current-controlled first phase, capacitive discharge second phase waveforms of both cathodic-first and anodic-first polarity. We monitored the concentration of platinum in solution under different stimulation delivery conditions including charge-balanced, charge-imbalanced, and monophasic pulses.

Main results—We observed that platinum dissolution decreased during charge-imbalanced and monophasic stimulation when compared to charge-balanced waveforms.

Significance—This observation provides an opportunity to re-evaluate the charge-balanced waveform as the primary option for sustainable neural stimulation.

Keywords

neuromodulation; electrical stimulation; neurostimulation safety; charge balance; medical devices

1. Introduction

Electrical neurostimulation is a rapidly expanding line of therapy for an increasing number of neurological and physiological disorders (Pikov 2015). Future neuromodulation devices will employ a number of innovations such as microelectrodes (Rajan *et al* 2015) and waveforms of unconventional shape and current steering to enable higher spatial resolution (Firszt *et al* 2007). Progress in this field is dependent on the contemporary regulatory landscape enabling rapid patient access to the most physiologically-effective, power-efficient, and safe therapies available.

A number of limitations for safe electrical stimulation of neural tissue have been outlined in the literature (Merrill *et al* 2005, Cogan *et al* 2016). Proposed limits on waveform shape, charge per phase and charge density are based on observations from experiments in animals in which damage to neural tissue was observed at relatively high levels of electrical stimulation (Pudenz *et al* 1975, McCreery *et al* 1990). Several theories were proposed to explain the mechanism of tissue damage, including ‘overstimulation’ (excitotoxicity) due to damage from ionic imbalances, excessive neurotransmitter release, and metabolic stress; and damage from noxious electrochemical species generated during charge injection (Krauthamer *et al* 1991). Since the contribution of each of these factors is not very well understood, the existing stimulation limits are based on purely empirical observations (Shannon 1992). The empirical nature of this limit makes it hard to extrapolate to stimulation paradigms that are substantially different from the conditions that were initially used to establish this limit. One classical requirement is for a non-injurious stimulation waveform to be biphasic and charge-balanced, first proposed by Lilly *et al* (1955). The traditional hypothesis states that a charge-balanced waveform is less damaging to tissue than charge-imbalance waveform, because electrochemically generated and potentially toxic species produced during the first phase of the waveform are consumed during the second phase of the waveform (Merrill *et al* 2005). However, very few studies have been performed to verify this hypothesis (Kumsa *et al* 2016a). Additionally, the charge-balanced concept has been challenged by *in vivo* studies by Mortimer and colleagues (Mortimer *et al* 1980, Scheiner *et al* 1990).

In this work, we investigated how charge-imbalance (less charge in the secondary phase) affects the generation of soluble platinum species. The dissolution of Pt electrodes occurs during charge injection on Pt and Pt-containing electrodes. Pt dissolution is an irreversible and undesirable electrochemical reaction (Agnew *et al* 1977, Robblee *et al* 1983). Our data demonstrates that charge-imbalance leads to a decrease in Pt dissolution during both cathodic-first and anodic-first pulses. This is an important observation that questions the established charge-balanced dogma and highlights the need for a more detailed evaluation of potential application of charge-imbalance waveforms in neurostimulation.

2. Methods

2.1. Chemicals

All chemicals were purchased from Sigma-Aldrich (Sigma Aldrich, St Louis, MO) and used as received. All experiments were performed with the solution (0.2 mg ml^{-1}) of bovine serum albumin (BSA) in phosphate-buffered saline (PBS) that was prepared using deionized water (18 M Ω cm Milli-Q). The solution was exposed to ambient atmosphere assuming equilibrium of the dissolved gases.

2.2. Electrochemical Experiments

Prior to each experiment, a Pt disk electrode with a diameter of 0.1 cm and area of 0.00785 cm² (ET075-1, eDAQ, Colorado Springs, CO) was polished on an aluminum oxide tile for 5 min and sonicated in deionized water for 3 min to ensure identical initial conditions. Measurements were performed in an open-to-atmosphere electrochemical H-cell (RRPG060, Pine Instrument, Durham, NC) at room temperature with 20 ml of PBS at pH 7.4 with BSA solution (Robblee *et al* 1980) in each compartment. The working electrode was placed in one compartment of the H-cell, and a Ag/AgCl reference electrode (930-00015, Gamry Instruments, Warminster, PA) and a graphite sheet counter electrode (Alfa Aesar, Ward Hill, MA) were placed in the other compartment of the H-cell (figure 1(A)).

Pulsing experiments were carried out using a Current-Pulse Capacitor Discharge instrument (CPCDi) manufactured at Case Western Reserve University (Kumsa *et al* 2016b). For charge-balanced waveforms, passive capacitive discharge was performed using a 1 μF capacitor. For charge-imbalance waveforms, a 100 Ω leakage resistor was used in parallel with the capacitor. For monophasic pulsing, a diode rectifier was employed to allow current to flow only in one direction. The detailed description of the instrument is provided elsewhere (Kumsa *et al* 2016b). The pulsing was done at 50 Hz with a 100 μs pulse width and 100 μs inter-phase delay. Biphasic charge-balanced, charge-imbalance and monophasic stimulations were investigated (figure 1(B)). A Tektronix oscilloscope (DPO 4034) with 10 M Ω input impedance probes was used for recording current and potential waveforms during pulsing measurements. The current amplitude varied from 1.73 mA to 12.56 mA, which corresponds to charge density of 22, 47, 77, 114 and 160 $\mu\text{C cm}^{-2}$ per phase. This range of charge densities was chosen to cover a region of interest for stimulation parameters from $k = 0.566$ to $k = 2.33$ as defined by the Shannon equation (Shannon 1992). Each experiment was run for two hours. The level of charge imbalance was calculated by integrating recorded current versus time traces (figure 1(B)) and yielded 15% for cathodic-first and 18.2% for anodic-first biphasic pulses. For control experiments, the working electrode was left at open circuit potential. The experiments for each set of parameter were replicated three times.

2.3. Inductively coupled plasma mass spectrometry (ICP-MS)

Aliquots of the solution were taken from the H-cell compartment with the Pt disk working electrode at the end of the each run (figure 1(A)). ICP-MS analysis was performed using a 2% nitric acid matrix on a Thermo Scientific X series 2 ICP-MS instrument (Thermo Scientific, Waltham, MA). Pt concentration was converted into dissolution rate expressed in units of $\mu\text{g cm}^{-2}$.

2.4. Data analysis

Data were processed and plots were generated using MS Excel (Microsoft, Redmond, WA) and Origin (OriginLab Corporation, Northampton, MA). All data are reported as mean and standard deviation.

3. Results

For the cathodic-first charge-balanced waveforms (figure 2(A)), the Pt dissolution increased with stimulation intensity up to $1.54 \pm 0.44 \mu\text{g cm}^{-2}$ after two hours for a charge injection level of $160 \mu\text{C cm}^{-2}$. Also, variability in measured Pt increased for higher charge injection values. When charge-imbalanced waveforms were used under the same conditions, Pt dissolution significantly decreased with a maximum dissolution of $0.218 \pm 0.016 \mu\text{g cm}^{-2}$ after two hours of stimulation at $160 \mu\text{C cm}^{-2}$. Cathodic monophasic pulsing led to an even smaller amount of Pt released into the solution with a maximum dissolution of $0.078 \pm 0.029 \mu\text{g cm}^{-2}$ after two hours of stimulation at $160 \mu\text{C cm}^{-2}$.

For the anodic-first charge-balanced waveforms (figure 2(B)), Pt dissolution followed the same pattern of increasing dissolution rate with stimulation intensity, reaching a maximum of $4.42 \pm 1.72 \mu\text{g cm}^{-2}$ after two hours of stimulation at $160 \mu\text{C cm}^{-2}$. Similar to the cathodic-first waveforms, the variability increased at higher Pt concentration, which follows the pattern that was reported earlier (Robblee *et al* 1980). The charge-imbalanced waveform led to a decrease in Pt dissolution with a maximum dissolution rate of $0.22 \pm 0.02 \mu\text{g cm}^{-2}$ after two hours of stimulation at $160 \mu\text{C cm}^{-2}$. Conversely, the anodic-first monophasic waveform resulted in a slightly higher rate than imbalanced with Pt released to the solution with a maximum dissolution of $0.93 \pm 0.06 \mu\text{g cm}^{-2}$ for two hours of stimulation at $160 \mu\text{C cm}^{-2}$.

4. Discussion

The use of charge-imbalanced waveforms to reduce electrode corrosion under cathodic-first pulses has previously been discussed in the literature (Scheiner *et al* 1990, Merrill *et al* 2005). Additionally, Pt dissolution during pulsing has been reported (Brunner *et al* 1977, Black and Hannaker 1979, McHardy *et al* 1980, Robblee *et al* 1980). Early work by McHardy *et al* (1977) demonstrated that cathodic charge imbalance reduces corrosion of stainless steel electrodes. However, direct relationship between charge-imbalanced waveform and its effect on irreversible electrochemical reactions such as Pt electrode dissolution under both cathodic-first and anodic-first pulses has not yet been established.

Our findings indicate that, for charge-balanced waveforms, Pt dissolution occurs over a wide range of charge densities including those in the region where the risk of tissue damage is considered to be minimal. For example, stimulation at charge density below $77 \mu\text{C cm}^{-2}$ and charge per phase of $0.6 \mu\text{C}$ for 0.1 cm diameter electrode ($k = 1.66$) places it in the region where no tissue damage was reported during brief stimulation in feline cortex (Pudenz *et al* 1975, McCreery *et al* 1990, Shannon 1992, Cogan *et al* 2016). The experiments were performed only for two hours, which makes it difficult to make predictions of the temporal profile of Pt release for a longer period of time. Furthermore, *in vivo* studies of Pt release

during electrical stimulation have shown that the rate of Pt release does not follow monotonic behavior (Robblee *et al* 1983) with the glial capsule likely to provide a barrier for Pt diffusion further from the electrode into the tissue (Roitbak and Syková 1999, Prodanov and Delbeke 2016).

Interestingly, our data indicates larger release of Pt in case of anodic-first stimulation versus cathodic-first stimulation. Cathodic-first is generally considered as more efficient in evoking action potentials than anodic-first (Merrill *et al* 2005). Our results suggest that the sequence in stimulation polarity plays an important role not only in its electrophysiological effects, but also in the generation of potentially-noxious electrochemical species. Hence, the sequence of stimulation polarity might be an important factor in evaluation of its safety.

The charge-balanced requirement for clinical neurostimulation is based on the assumption that fewer products of irreversible electrochemical reactions are produced during charge-balanced stimulation. Our findings indicate the opposite behavior, with regards to Pt dissolution. For both charge-imbalanced and monophasic stimulation, less Pt is released in the solution for the experiments performed at the same charge density. Along with dissolution of Pt, other reactions such as reduction of oxygen with generation of reactive oxygen species (Morton *et al* 1994), oxidation of chloride and generation of oxychlorides (Brunner *et al* 1977), oxidation of endogenous compounds (Merrill *et al* 2005, Musa *et al* 2011) and electrolysis of water with shifts in pH and generation of hydrogen (H₂) and oxygen (O₂) are listed in the literature as potentially undesirable for neural tissue. The effect of charge-imbalance on these reactions needs to be further investigated to assess the potential of imbalanced waveform for clinical neurostimulation. Additional *in vitro* experiments are needed to fully characterize the effect of imbalanced waveforms on generation of other noxious species. This includes examination of electrochemical reactions occurring during pulsing. Additionally, investigation of charge-imbalance during neurostimulation *in vivo* in specific anatomic locations and with use of modern histological techniques is needed.

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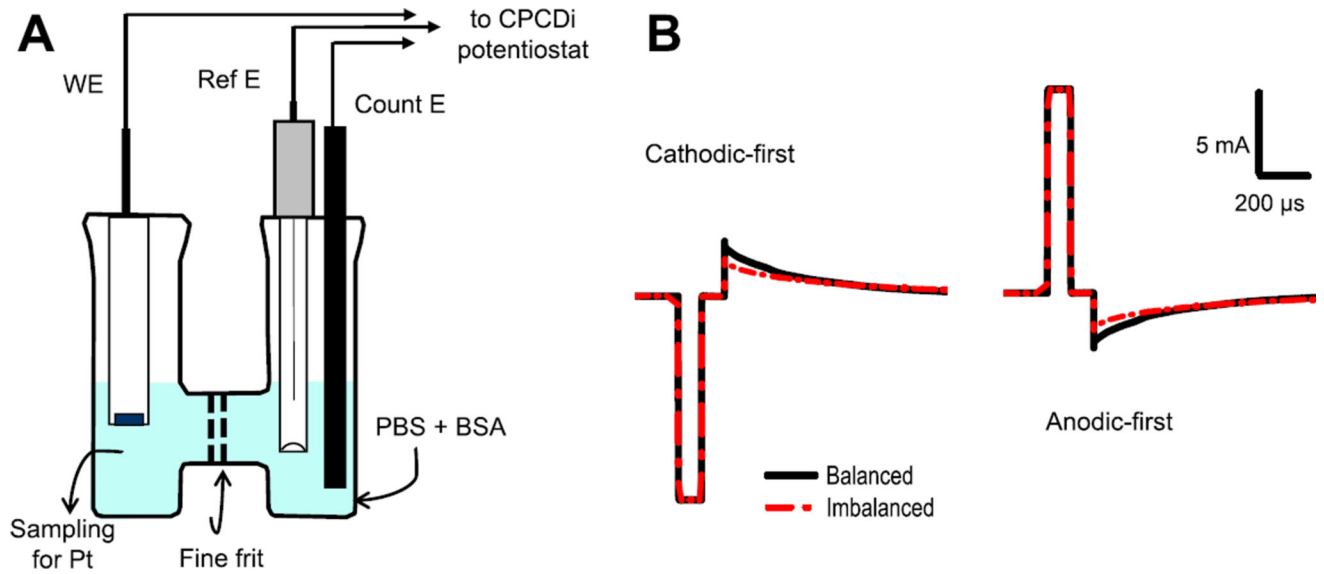


Figure 1. Experimental setup and sketch of the used waveforms. (A) Experiments were performed in an H-shaped bicameral cell filled with PBS solution of BSA with Ag/AgCl reference (Ref E) and carbon counter (Count E) electrodes located in the right compartment and Pt disk working electrode (WE) located in the left compartment where samples for ICP-MS analysis for Pt were taken at the end of pulsing. Current pulsing was performed with the CPCDi instrument at 50 Hz using capacitive discharge waveforms under both charge-balanced and charge-imbalanced conditions (B) in either cathodic-first or anodic-first configuration with 100 μ s pulse width and 100 μ s inter-phase delay.

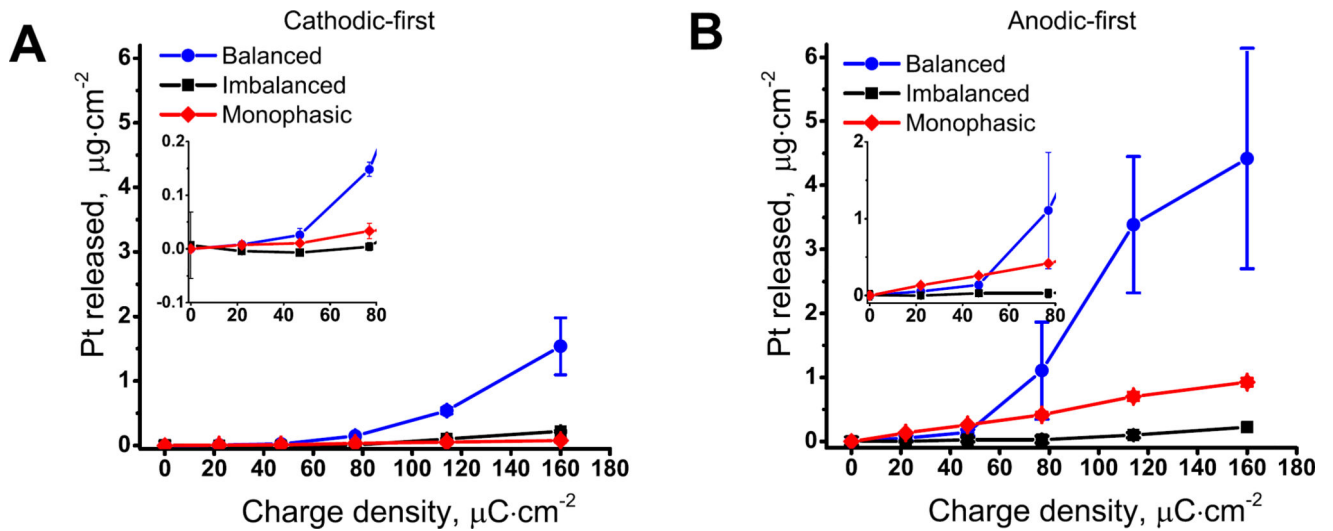


Figure 2. Concentration of platinum in solution under different stimulation conditions. Concentration of Pt measured with ICP-MS after two hours of pulsing for cathodic-first (A) and anodic-first (B) stimulation at different charge densities at frequency of 50 Hz. Data reported for three independent replicates as mean and standard deviation. The inserts show scaled data for charge densities up to $80 \mu\text{C cm}^{-2}$.