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Intraoperative direct cortical stimulation motor evoked potentials: Stimulus parameter recommendations based on rheobase and chronaxie

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HIGHLIGHTS

- Optimal direct cortical stimulation MEP parameters are the ISI with lowest *rheobase*^{2} $\times$ *chronaxie*, and D at its chronaxie.
- Based on 20 patients, 4 ms ISI and 0.2 ms D are most consistently optimal or near-optimal.
- Two-point rheobase and chronaxie estimation is accurate enough for quick individual optimization.

ABSTRACT

Objective: To determine optimal interstimulus interval (ISI) and pulse duration (D) for direct cortical stimulation (DCS) motor evoked potentials (MEPs) based on rheobase and chronaxie derived with two techniques.
Methods: In 20 patients under propofol/remifentanil anesthesia, 5-pulse DCS thenar MEP rheobase and chronaxie with 2, 3, 4 and 5 ms ISI were measured by linear regression of five charge thresholds at 0.05, 0.1, 0.2, 0.5 and 1 ms D, and estimated from two charge thresholds at 0.1 and 1 ms D using simple arithmetic. Optimal parameters were defined by minimum threshold energy: the ISI with lowest *rheobase*^{2} $\times$ *chronaxie*, and D at its chronaxie. Near-optimal was defined as threshold energy <25% above minimum.
Results: The optimal ISI was 3 or 4 (n = 7 each), 2 (n = 4), or 5 ms (n = 2), but only 4 ms was always either optimal or near-optimal. The optimal D was ~0.2 (n = 12), ~0.1 (n = 7) or ~0.3 ms (n = 1). Two-point estimates closely approximated five-point measurements.
Conclusions: Optimal ISI/D varies, with 4 ms/0.2 ms being most consistently optimal or near-optimal. Two-point estimation is sufficiently accurate.
Significance: The results endorse 4 ms ISI and 0.2 ms D for general use. Two-point estimation could enable quick individual optimization.

1. Introduction

One elicits intraoperative direct cortical stimulation (DCS) muscle motor evoked potentials (MEPs) with a short train of monophasic rectangular electrical pulses having a user-selected interstimulus interval (ISI) and pulse duration (D). While practitioners commonly choose 4 ms ISI and 0.5 ms D, reported parameters vary and none have been proven optimal, leaving no consistent scientific rationale for the selection (Taniguchi et al., 1993; Cedzich et al., 1996; Kombos et al., 2000; Neuloh et al., 2004; Kombos et al., 2009; Kamada et al., 2009; Szelényi et al., 2010; Nossek et al., 2011). Basing the choice on rheobase and chronaxie would be

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physiologically sound, but there are no previous reports of their values for human DCS MEPs.

Rheobase ('current' + 'foundation') is asymptotic threshold current at infinite D and chronaxie ('time' + 'axis') is an excitability time constant defined by D at which threshold current is twice the rheobase (Geddes, 2004; Prutchi and Norris, 2005). They are usually derived by linear regression of threshold charge (*current* $\times$ *D*) at several D, with the resulting slope and x intercept yielding the rheobase and chronaxie (Weiss, 1901; Geddes, 2004; Prutchi and Norris, 2005; Brunel and van Rossum, 2007). Fig. 1 illustrates strength–duration principles and shows how minimizing threshold energy ($current^2 \times D \times resistance$) with D = chronaxie can be considered optimal.

Threshold energy is a function of rheobase and chronaxie, which may vary with ISI (Szelényi et al., 2007a; MacDonald et al., 2013). If so, then one could define optimal DCS MEP parameters as the ISI having rheobase and chronaxie resulting in minimal threshold energy, and D at its chronaxie.

If optimal parameters vary between patients, then individual rheobase and chronaxie-based optimization might be useful. To do so, measuring several thresholds and performing linear regression would be time-consuming, but the linear charge–duration relationship might allow sufficiently accurate and faster two-point estimation using simple arithmetic.

This study's primary objectives were to determine optimal parameters for DCS thenar MEPs based on rheobase and chronaxie measured with linear regression, and to assess the feasibility of an arithmetical two-point estimation method.

2. Methods

Our hospital's Research Advisory Committee approved the study as being in accordance with the declaration of Helsinki and its later amendments. All patients gave verbal informed consent. The sample size was set to 20 based on a preliminary power analysis.

2.1. Patients

Candidates were patients of any age, gender or ethnicity undergoing peri-Rolandic brain surgery with DCS MEPs for clinical reasons and having ≥4/5 preoperative contralateral arm strength. Of 22 candidates, one was excluded because of unclear localization of motor cortex away from the craniotomy, and another was excluded due to an intraoperative seizure before threshold testing could be done. Of the 20 included patients, there were 12 males and 8 females aged 8–55 years (median 26.5). Eighteen had a history of seizures. Ten were undergoing tumor resection and another 10 were undergoing resective epilepsy surgery for cortical dysplasia (5), cavernous hemangioma (2), tumor (2), or a neuroimaging-negative focus (1). The lesions or epileptic foci were frontal (10), parietal (6) or frontoparietal (4); 18 were lateral, 2 were mesial and 7 involved the primary motor gyrus. Nineteen patients had 5/5 preoperative arm strength and one had grade 4/5 weakness.

2.2. Stimulator

We used a Nicolet Endeavor™ constant-current stimulator for 5-pulse DCS. Train frequency determined ISI and was adjustable from 2 to 500 Hz with 1 Hz granularity. We chose built-in presets of 500, 350, 250 and 200 Hz for testing ISIs of 2, ~3 (actually 1000/350 = 2.86), 4 and 5 ms. Similarly, D was adjustable from 0.01 to 1 ms with 0.001 ms granularity and we chose built-in presets of 0.05, 0.1, 0.2, 0.5 and 1 ms for testing. With a biomedical engineer applying precise resistance and measurement, calibration of 10 mA output across 4 kΩ resistance confirmed nearly exact ISI, D and first-pulse peak current at each of the 20 test parameter combinations, and quantified the stimulator's downward output ramps (Fig. 2).

The device's maximum output could be preset to any level up to 100 mA. The step size of the intensity-adjustment dial was the selected maximum/100, and the resulting 1 mA steps with a 100-mA maximum were too large for precise threshold measurement. Consequently, to enhance resolution with smaller steps (e.g.,

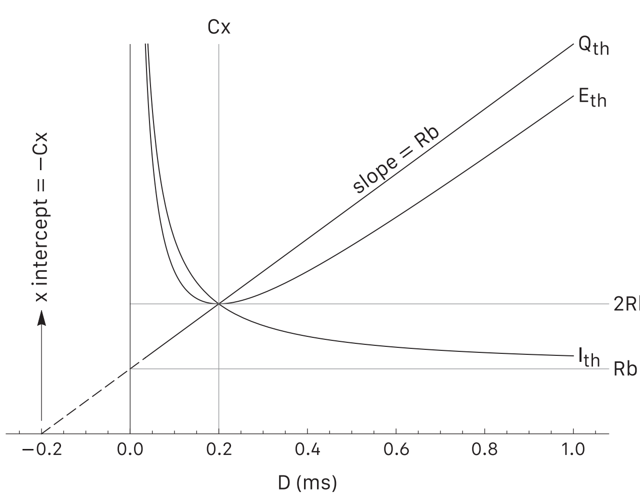

Fig. 1. General strength–duration plots modeled with 0.2 ms chronaxie (Cx). Rheobase (Rb) is current threshold (I_{th}) at infinite pulse duration (D) and Cx is D at which I_{th} = 2 Rb. Charge threshold (Q_{th}) rises linearly with D; its slope and extrapolated x intercept equal Rb and −Cx. I_{th} and energy threshold (E_{th}) drop sharply from high values at D < Cx. I_{th} then levels off towards Rb with D > Cx, while E_{th} reaches a minimum at D = Cx and rises again with D > Cx. Thus, D < Cx constrains charge at the expense of high current and energy, and D > Cx constrains current at the expense of high charge and energy. However, D = Cx minimizes energy while balancing modest charge and current, and can therefore be considered optimal.

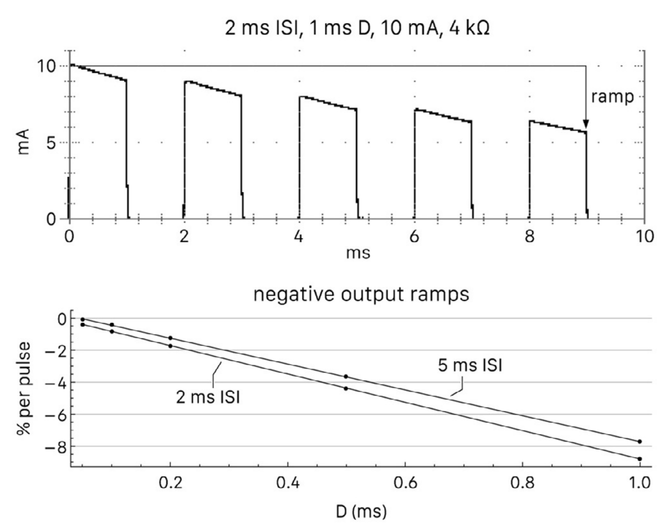

Fig. 2. Stimulator calibration. Oscilloscopic calibration (top panel screen dump) confirmed nearly exact interstimulus interval (ISI), pulse duration (D) and first-pulse peak current output at each parameter combination, with downward output ramps that accumulated across the train. The negative ramps (bottom panel) increased linearly with D, and to a lesser extent with shorter ISI. They were negligible at 0 to −2% per pulse with ≤0.2 ms D but more substantial with 0.5 and 1 ms D at around −4% and −8% per pulse; the top panel shows the maximum observed decay.