Clinical Neurophysiology xxx (2015) xxx–xxx

Contents lists available at ScienceDirect

Clinical Neurophysiology

journal homepage: www.elsevier.com/locate/clinph

A comparative study of the effects of pulse parameters for intracranial direct electrical stimulation in epilepsy

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ARTICLE INFO

Article history:
Accepted 13 February 2015
Available online xxxx

Keywords:
Single-pulse electrical stimulation
Drug-resistant epilepsy
Stereoelectroencephalography

HIGHLIGHTS

- The effects of variable pulse duration, intensity, phase, and polarity were studied.
- A key feature is the multi-parametric stimulation on the same stereo-EEG contacts.
- The common factor driving the magnitude of the EEG responses is the applied charge/phase.

ABSTRACT

Objectives: Intracranial direct electrical stimulation (iDES) uses different parameters for mapping the epileptogenic and functional areas in patients with drug-resistant epilepsy. We aim at finding the common factor driving the electrographic responses to various iDES protocols reported in the literature.
Methods: We recorded early responses to single-pulse iDES in 11 subjects undergoing stereoelectroencephalographic presurgical evaluation. We systematically explored the role of several pulse parameters in evoking responses: monophasic versus biphasic pulses, current intensity, and pulse duration. We performed a correlation and regression analysis between responses to different protocols by amplitude, duration, and charge per phase.
Results: Regression analysis revealed that the responses were similar for the same charge per phase, regardless of their pulse duration and amplitude. Over eighty percent (82.8%) of the responses to variable pulse duration biphasic stimulation and between 58.6% and 81.9% of the responses to monophasic stimulation, depending on pulse polarity, were correlated to the responses evoked by the variable amplitude biphasic protocol, when expressing stimulus strength in terms of charge per phase.
Conclusions: Regardless of the combination of different stimulation currents, it is the underlying charge per phase parameter that determines the magnitude of the responses to single-pulse electrical stimulation.
Significance: Our results provide a unifying method for comparing iDES protocols.

1. Introduction

Patients with drug-resistant epilepsy undergoing presurgical evaluation are often investigated using intracranial direct electrical stimulation (iDES), in addition to recording the spontaneous electroencephalographic (EEG) activity. Cortical regions and/or axonal tracts are directly stimulated using subdural grids or depth electrodes, in order to evoke responses that help in delineating the epileptogenic network and eloquent cortex. Different protocols are used in practice to either evoke after-discharges or obtain clinical responses. However, for the purpose of this study, we focus only on subclinical stimulation protocols and analyze the EEG responses for different pulse parameters. This approach allows us to objectively evaluate the efficacy of the stimulation by performing a

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http://dx.doi.org/10.1016/j.clinph.2015.02.013
1388-2457/

quantitative analysis of the EEG responses rather than relying on the subjective perception of the clinical responses evoked by iDES.

One of the most widely used protocols for subclinical stimulation is the single-pulse electrical stimulation (SPES), first introduced by Valentin and colleagues in 2002 (Valentin et al., 2002). Since then, it has been used either in chronic setup for presurgical investigations using depth and/or subdural electrodes (Valentin et al., 2005a,b; Lacruz et al., 2010; Flanagan and Valentin, 2009; van't Klooster et al., 2011; Matsumoto et al., 2004, 2007), or during intraoperative mapping of the epileptogenic zones (Kokkinos et al., 2013). The single-pulse term is often used to denote protocols where pulses are spaced at least 5 s apart, as originally introduced by Valentin et al., 2002, but it is often extended to cover low-frequency 1-Hz repetitive stimulation (David et al., 2008, 2010, 2013; Boido et al., 2014). Stimulation with pulses spaced at least 5 s apart has been shown to be below the threshold for evoking clinical responses, even with currents as high as 8 mA (Kokkinos et al., 2013). There is only one notable exception to this general finding, reported by Lacruz et al. (2010) in a very particular configuration, where bilateral SPES applied to the hippocampal formation was shown to result in a transient impairment in episodic memory. However, the same study shows that unilateral stimulation with the same levels failed to evoke any clinical response, in accordance with the other experiments reported in the literature and for our present study as well. This situation does not extend to the 1-Hz stimulation that has been part of the routine clinical investigation for decades, and it has been known to evoke afterdischarges (Munari et al., 1993), clinical responses (Kahane et al., 1993; Rubboli et al., 2006), and buildup of activity during stimulation, which has been associated with cortical plasticity (David et al., 2008). An inter-pulse interval >5 s, as large as 15 s in our study, should allow for the network to return to its resting state, such that the responses to successive pulses can be considered independent from each other.

Due to its properties to evoke electrographic responses in the absence of clinical responses, SPES is considered an important tool for mapping functional connectivity between different brain regions (Matsumoto et al., 2004; Catenoix et al., 2005; David et al., 2013) and cortical excitability (Iwasaki et al., 2010; Enatsu et al., 2012a,b; Freestone et al., 2011; Barborica et al., 2014).

The parameters that are commonly listed as most indicative of the strength of the stimulation are current amplitude, frequency of stimulation, and eventually pulse width. However, the current density, which depends on the contact surface, the pulse width, the phase, and the polarity of the pulses, as well as the charge density and charge per phase equally contribute to the efficacy of the stimulation (Donos et al., 2013). In a review, David et al. (2010) surveyed a significant number of papers on iDES that used stimulation protocols with different pulse types, pulse amplitudes, and pulse durations. Although some of these stimulation protocol parameters partially overlapped (e.g., Valentin et al. (2002) used monophasic square wave pulses with a 1-ms duration and 1–8-mA current intensities, whereas Munari et al. (1993) and Kahane et al. (1993) used bipolar square wave pulses with a 3-ms duration and up to 3-mA current intensity), there is no commonly accepted way of performing a direct comparison in terms of the efficacy of the different stimulation protocols, as assessed through the characteristics of the evoked responses.

Our study's goal is to perform a systematic investigation of the differences between the effects of three pulse parameters (phase, duration, and amplitude), in order to find the common denominator of the various different stimulation protocols reported in the literature. We use SPES as a tool for performing this multi-parametric investigation, as it has been shown to minimally perturb the brain networks, and it is unlikely to evoke clinical responses for commonly used parameters.

2. Patients and methods

Our study is based on 11 patients (four males, seven females, mean age 31, range 11–47 years) with drug-resistant epilepsy (Table 1). Patients gave their informed consent, and the entire investigation was performed under ethical committee approval No. 2621/03.02.2012.

On average, 13 depth electrodes (range 9–17) were implanted in the left or right hemisphere, depending on the pathology. Eight implantation procedures were performed using a Leksell stereotactic frame, and the other three procedures were performed using a stereotactic fixture mT Platform (FHC Inc., Bowdoin, ME, USA), which is custom-made to fit the patient's anatomy and allows bilateral implantations using both orthogonal and oblique electrode trajectories (Balanescu et al., 2014).

Data acquisition was performed using a CareFusion Nicolet EEG Wireless Amplifier. We recorded EEG signals using a montage of 64 contacts carefully selected by the epileptologist after reviewing the activity from all the available contacts on all the implanted depth electrodes, based on their pathological activity and relevance for delineating the resection limits and eloquent cortex. The sampling rate was set to 4096 Hz. High-pass and low-pass filters were disabled during data acquisition.

For electrical stimulation, we used a programmable clinical stimulator (Guideline LP+, FHC Inc.) that allows the definition of complex and even arbitrary waveforms. We defined the following three stimulation protocols: biphasic single-pulse electrical stimulation (BSPES), monophasic single-pulse electrical stimulation (MSPES), and variable pulse duration electrical stimulation (VPDES), as shown in Fig. 1.

BSPES consists of 20-square biphasic pulses, a 3-ms pulse duration, having a variable amplitude in the range of 0.25–5 mA (Fig. 1a). The inter-pulse interval was chosen as 15 s (0.067 Hz), long enough to allow a resetting of the brain networks in the interval between successive pulses. MSPES (Fig. 1b) uses monophasic pulses of alternating polarity, having the same amplitude, pulse duration, and inter-pulse interval. The number of applied stimulation pulses is 40 (20 positive pulses and 20 negative pulses), each positive pulse being followed 15 s later by a negative one having the same amplitude, to preserve the injected charge balance. For both BSPES and MSPES, the stimulation current was pseudo-randomly varied in the 0.25–5-mA range (with a 0.25-mA step) in order to decouple time and stimulus amplitude factors when performing a statistical significance analysis of the responses.

VPDES consists of 12-square biphasic pulses having a constant amplitude of 5 mA, a 15-s inter-pulse interval, and a pseudo-random pulse width in the 0.25–3-ms range (a 0.25 ms step), as shown in Fig. 1c.

For each stimulation trial, regardless of the protocol used, we stimulated on two adjacent contacts from the same electrode, and we recorded raw data in a referential montage from the other 62 contacts. An example of an implantation scheme is featured in Fig. 2, where the contacts included in the recording montage ($n = 64$) are highlighted in green, while the rest of the unused contacts are shown in red. Between 33 and 93 stimulation trials were applied to each patient, of which 13–30 were BSPES stimulations. For all patients, for each BSPES stimulation trial, we also tested the same contact pair with MSPES and VPDES, resulting in equal number of stimulation trials for all three protocols. We have calculated the charge per phase representing the product between the injected current and the pulse duration $Q = I \cdot t$ for all pulse parameters. All protocols have been covering the same range of charge per phase, as the maximal pulse parameters were identical, in terms of pulse duration $t_{max} = 3$ ms, current $I_{max} = 5$ mA, and charge per phase $Q_{max} = 15$ μC/phase. The only difference for pulses at the

Please cite this article in press as: Donos C et al. A comparative study of the effects of pulse parameters for intracranial direct electrical stimulation in epilepsy. Clin Neurophysiol (2015), http://dx.doi.org/10.1016/j.clinph.2015.02.013