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Can single pulse electrical stimulation provoke responses similar to spontaneous interictal epileptiform discharges?

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HIGHLIGHTS

- Patients have several spontaneous interictal epileptiform discharge (IED) patterns and the areas showing IEDs are more widespread and multifocal than the area of seizure onset zone.
- Delayed responses to single pulse electrical stimulation (SPES) are always similar to at least one IED pattern in the same patient and occur at or in the vicinity of the seizure onset zone.
- IEDs and SPES responses may share similar physiological mechanisms and the IEDs resembling delayed responses to SPES may be those IEDs associated with seizure onset.

ABSTRACT

Objective: To estimate the proportion of patients where EEG responses to single pulse electrical stimulation (SPES) are similar to spontaneous interictal epileptiform discharges (IEDs) in the same patient, and whether such resemblance is related to seizure onset.
Methods: We have visually compared the morphology, topography and distribution of IEDs and of SPES responses in 36 patients with intracranial EEG recordings during presurgical evaluation.
Results: Each patient showed between 3 and 17 different IED patterns, located at seizure onset zone and elsewhere. Only 13 patients showed the highest incidence and amplitude of IEDs at the site of focal seizure onset. Twenty-eight patients showed early responses which were similar to at least one IED pattern. Thirty patients showed delayed responses which were always similar to at least one IED pattern and were always located at seizure onset or in its vicinity.
Conclusions: Early SPES responses often, and delayed responses always, were similar to at least one IED pattern in the same patient. The IEDs resembling delayed responses were those associated with seizure onset.
Significance: The similarities between IEDs and SPES responses suggest that SPES can trigger the mechanisms responsible for generating IEDs, which may become a tool to study the pathophysiology of IEDs.

1. Introduction

The value of interictal abnormalities in intracranial recordings during presurgical assessment has long been debated. Focal slowing tends to occur around the seizure onset zone (Valentin et al., 2014). In addition, intracranial recordings usually show several patterns of spontaneous interictal epileptiform discharges (IEDs) independently observed at the site of seizure onset and elsewhere, often on the opposite hemisphere (Alarcon et al., 1994; Fernandez Torre et al., 1999a). Consequently, the localizing power of IEDs is limited, since no clear criteria are available to identify those IEDs occurring at the epileptogenic zone.

Single pulse electrical stimulation (SPES) is a useful tool to identify the epileptogenic zone in the interictal period (Alarcon et al., 2012; Flanagan et al., 2009; Valentin et al., 2005a,b, 2002). Direct cortical stimulation with a single electrical pulse of 1-ms duration

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is associated with two types of cortical EEG responses: early and late responses. Early responses consist of a sharp deflection occurring immediately after the stimulus artifact or merging with it, followed by a slow wave. Since early responses are seen when stimulating most cortical areas, either locally or over regions connected to the stimulated cortex (Lacruz et al., 2007; Rosenzweig et al., 2011), they probably represent normal cortical responses to SPES.

Late responses arise after the early response and they are of two types: delayed and repetitive responses. Delayed responses consist of one or several spike-and-slow waves, resembling interictal epileptiform discharges with a delay longer than 100 ms. after stimulation. Repetitive responses are seen mainly when stimulating frontal structures (Valentin et al., 2005a). They consist of two or more consecutive waves, each resembling the initial early response. Regions generating repetitive responses and areas showing delayed responses tend to be those originating seizures and their removal is a good predictor of postsurgical seizure control in adults and children (Flanagan et al., 2009; Valentin et al., 2005b).

IEDs and early responses to SPES share a number of characteristics. Both, IED and early responses:

(a) Consist of a spike or sharp wave followed by a slow wave (Valentin et al., 2002)
(b) Can be associated with memory impairment (Aarts et al., 1984; Lacruz et al., 2010).
(c) Are associated with similar changes in neuronal firing (burst, inhibition or burst followed by inhibition), suggesting that they are generated by similar physiological mechanisms (Alarcon et al., 2012, 2008).

In addition, we have anecdotally reported that delayed responses to SPES can resemble IEDs (Valentin et al., 2005a,b, 2002). However, it is unclear whether SPES responses specifically resemble the IEDs recorded in the same patient. In the present work, we estimate the proportion of patients where EEG responses to SPES are similar to the IEDs observed in the same patient. In order to establish if IEDs and responses to SPES show similar EEG features, we have visually compared the morphology, topography and distribution of IEDs and of SPES responses (early and late) within patients. Strong similarities between IEDS and responses to SPES would support that both phenomena share similar pathophysiological mechanisms. Moreover, the secondary objective of the present work is to establish whether the resemblance between SPES responses and IEDs can be an interictal marker for the seizure onset zone. Since delayed responses to SPES show a strong association with the epileptogenic zone, those IEDs resembling delayed SPES responses could constitute a biomarker for epileptogenicity.

2. Methods

2.1. Patients

We studied 36 consecutive patients (14 males, 22 females, mean age 33.97 years, range 14–53 years) assessed with intracranial EEG recordings during presurgical evaluation for the treatment of their epilepsy in the Department of Clinical Neurophysiology at King's College Hospital. Patients suffered from medically refractory epilepsy and were admitted for video-EEG monitoring with intracranial electrodes because reliable localization of the epileptogenic zone had not been achieved by non-invasive tests. The experimental procedure for SPES was initially approved by the Ethical Committee of King's College Hospital (reference number 99-017) and has now become a standard clinical protocol in our centre.

2.2. Electrode placement

Subdural or intracerebral (depth) electrodes were implanted in all 36 patients. The type, number and location of the electrodes were determined by the suspected location of the ictal onset region, according to non-invasive evaluation: clinical history, scalp EEG recordings obtained with the Maudsley system (Alarcon et al., 2001; Fernandez Torre et al., 1999b; Kissani et al., 2001), neuropsychology (Akanuma et al., 2003) and neuroimaging. All 36 patients had electrodes located in temporal areas. Fourteen had additional electrodes located in frontal areas, eight had electrodes located in occipital areas, and eight had electrodes located in parietal areas. Thirty patients had electrodes implanted bilaterally and six had electrodes restricted to one hemisphere. The selection criteria and implantation procedure have been described elsewhere (Alarcon et al., 2009).

2.2.1. Subdural electrodes

Electrode strips or mats (AdTech Medical Instruments Corp., WI, USA) were used in 27 patients. Each strip consisted of a single row of 4–8 platinum disk electrodes spaced at 10 mm between centers. The disks were embedded in a 0.7 mm thick polyurethane strip which overlapped the edges leaving a diameter of 2.3 mm exposed, and recessed approximately 0.1 mm from the surface plane. Mats contained rectangular arrays of 12, 16, 20, 32 or 64 similar platinum electrodes with 10 mm center-to-center distances within rows.

2.2.2. Intracerebral (depth) electrodes

In 9 patients, bilateral multicontact flexible bundles of depth electrodes (AdTech Medical Instruments Corp., WI, USA) were implanted stereotactically under MRI guidance. The electrode bundles contained 6–10 cylindrical 2.3 mm long platinum contacts separated by 5 mm between centers of adjacent electrodes of the same bundle. Among these 9 patients, 4 had bilateral electrodes restricted to temporal structures, 3 patients had bilateral temporal and unilateral occipital electrodes, and two patients had electrodes implanted bilaterally in frontal and temporal structures.

2.3. EEG recording

Recording of intracranial EEG started when the patient had recovered from electrode implantation, usually 24–48 h after surgery. Cable telemetry with up to 64 recording channels was used for data acquisition with simultaneous video monitoring. In 34 patients a Telefactor Beehive-Beekeeper system (Astro-Med, RI, USA) was used. Data were digitized at 200 Hz and band pass filtered (high pass cut-off frequency at 0.3 Hz and low pass cut-off frequency at 70 Hz). The system input range was 2 mV and data were digitized with a 12 bit analog-to-digital converter (amplitude resolution of 0.488 μV). In the remaining two patients, a Medelec-Profile system was used (Medelec, Oxford Instruments, United Kingdom). Data were digitized at 256 Hz and band pass filtered (0.05–67 Hz). The input range was 10 mV and data were digitized with a 22 bit analog-to-digital converter (an amplitude resolution of 0.153 μV). Data were recorded as common reference to Pz or to an intracranial electrode and displayed in a variety of montages including common average reference. When common average reference was used, channels showing large spikes, artifacts or responses were removed from the average.

2.4. Experimental protocol and analysis

SPES was performed between adjacent electrodes using a constant-current neurostimulator (Medelec ST10 Sensor, Oxford Instruments, United Kingdom). Electrical stimulation was carried